Intensive Care Med (1987) 13:89–95

Intensive Care Medicine

Review article

Organ dysfunction after cardiopulmonary bypass. A systemic inflammatory reaction initiated by the extracorporeal circuit

S. Westaby

Department of Surgery, Hammersmith Hospital and Royal Postgraduate Medical School, London, UK

Received: 1 August 1985; accepted: 18 February 1986

Since the first open heart operations in the 1950s cardiopulmonary bypass (CPB) has been known to contribute to the mortality and morbidity of cardiac surgery [1–3]. In 1985 when hospital mortality for some groups of patients is less than 1%, modern CPB seems well tolerated, yet as the scope of cardiac surgery extends to younger infants and older adults with more complex lesions, the probability of experiencing clinical manifestations of perfusion damage increases [4, 5]. Collectively these effects have been called the 'Post Perfusion Syndrome'. In its most pronounced form this consists of pulmonary and renal dysfunction, bleeding diatheses, neurological changes and fever of non-infective origin [6–10].

The overall consequence of the post perfusion syndrome is multiple organ dysfunction which may be transient and inconsequential as in most straightforward adult bypasses or alternatively, may necessitate prolonged respiratory or renal support, blood transfusion or re-entry for diffuse abnormal bleeding. Surgery for congenital heart disease in the first 3 months of life carries substantial mortality from perfusion related non-cardiac sequelae and it is notable that Lillehei's early results for correction of intracardiac defects in infancy using the child's mother as oxygenator achieved a success rate that took almost 25 years to emulate using CPB [11].

Cardiopulmonary bypass can never be truly physiological. The artificial environment created by plastics, glass and metal results in many alterations in structure and function of the blood which traverses the extracorporeal circuit and indirectly of the tissues of the body by virtue of these changes. Until recently there was no unifying hypothesis to explain the complex cellular and hormonal events occurring in response to contact of blood with allegedly 'biocompatible' surfaces. Organ damage was largely attributed to microembolism and the byproducts of protein denaturation [2, 12, 13]. This led to developments in membrane oxygenation and blood filtration which have made significant steps in prevention of cerebral damage but less so for other systems. In 1981 at the University of Alabama it was suggested that the generalized interstitial oedema, fever and leucocytosis in infants after bypass resembled the acute inflammatory response at a local site of injury [6].

Post-operative pyrexia of 2 or 3 days duration is an invariable finding after cardiac surgery with cardiopulmonary bypass. Closed cardiac procedures without extracorporeal circulation have no such sequelae and there is no evidence whatever that this pyrexia is of an infective nature [14]. This stimulated the concept of a whole body inflammatory response directed against materials of the extracorporeal circuit and for the first time suggested activation, (rather than denaturation) of various humoral cascades with resulting cellular changes [6]. In retrospect it was naive to believe we could continuously re-circulate a patient's blood through a complex extracorporeal circuit without initiating some form of host defence reaction.

Pump lung

Though coagulation disorders, cerebral and renal dysfunction have been studied exhaustively, the lungs most frequently manifest perfusion related injury and have produced most information implicating mechanisms of membrane damage.

There is now considerable evidence to suggest that CPB produces changes in the lungs that are qualitatively different from those produced during other surgical procedures [15]. 'Pump lung' ranges from barely noticeable interstitial oedema to rare but lethal haemorrhagic pulmonary oedema. This results in increased work of breathing, arterial hypoxaemia with increased alveolar arterial oxygen difference and in-

creased fluid in the tracheobronchial tree. There is shunting due to both venous admixture and alveolar collapse. Total air flow resistance increases and there are measurable changes in pulmonary compliance [16]. These changes in mechanical properties have been ascribed in part to non-cardiogenic increases in extravascular lung water. In normal lungs interstitial oedema does not create serious gas exchange problems but after major surgery reduced compliance and the increased work of breathing may lead to prolonged intubation, increased risk of infection and a pulmonary death. In practice, assessment of small accumulations of extravascular lung water (EVLW) is difficult. Snashall has suggested that EVLW must increase by 100% before becoming clinically detectable and the chest radiograph becomes abnormal only when lung water increases more than 30% [17]. However, modern techniques using computerized thermal green dye double indicator dilution, radionucleotide double indicator techniques and measurement of transthoracic electral impedance do demonstrate significant increases of EVLW routinely after CPB. It could be suggested that such changes occur as a result of haemodynamic alterations such as left heart failure, but Boldt and co-workers could find no relationship between EVLW and haemodynamic variables [18] whilst Royton has demonstrated increased permeability of the alveolar capillary barrier in CPB patients [19].

Both light and electron microscopy have shown consistent pathological changes in ultrastructure in lung biopsies from surviving patients up to 4 h after bypass [20, 21]. There is an overwhelming engorgement of the pulmonary vascular bed, microatelectasis and both interstitial and alveolar haemorrhage. There is damage and swelling (intracellular oedema) of capillary endothelial cells affecting the matrix compartment of the mitochondria and the endoplasmic reticulum. There is pronounced interstitial oedema which is often severe. The pericapillary space shows dispersion and there is an accumulation of leucocytes with their degranulation products in apposition to the capillary membrane with local endothelial damage. There is oedema and rarefaction of the cytoplasm within type I pneumocytes. Interstitial mast cells show loss in density and degranulation. These ultrastructural changes have been correlated with duration of perfusion.

The aetiology of pulmonary damage has been widely debated. Embolisation of particulate debris was one of the first theories and early studies implicated intravascular microaggregation of platelets and leucocytes resulting in mechanical destruction [22]. Without filters the lung is the primary filter for intravascular emboli during partial bypass with the lungs in circuit. Filters in the arterial, venous and cardiotomy suction lines reduce the incidence of embolisation but do not prevent subsequent pulmonary dysfunction.

On total bypass the lung is hypoperfused and not ventilated but left partially inflated with 100% oxygen. This may be regarded as a form of controlled organ shock to the lung. The lack of blood supply with subsequent damage to type II pneumocytes produces a decrease or total lack of surfactant production which could contribute to the development of pulmonary alveolar collapse [23]. However, Barratt-Boyes and Kirklin have both observed that the use of profound hypothermia and total circulatory arrest has diminished the incidence of pulmonary complications in infants after intracardiac procedures [24]. This implies that a shorter period of CPB gives a small dose of whatever causes post bypass pulmonary dysfunction. Kirklin identified susceptibility of the young infant to post perfusion pulmonary dysfunction as the primary reason for association of young age with increased hospital mortality after cardiac surgery [4].

The 'whole body' inflammatory response

Inflammation at a local site of vascular injury begins with platelet adherence and activation of the coagulation cascade to form a haemostatic plug. Chemotactic agents including complement derived anaphylatoxins are liberated attracting neutrophils and monocytes. Vasoactive substances cause tissue oedema.

When blood first contacts the foreign materials of the extracorporeal circuit platelets adhere to the surface. Hageman factor (XII) is activated initiating clotting and without heparin binding of antithrombin III, bypass could not continue. However, the humoral cascades are closely interlinked and Hageman factor also activates the Kinin-bradykinin system which in turn triggers the fibrinolytic system and the complement cascade [25]. Without the moderating capability of circulating protease inhibitors a massive anaphylactoid reaction would occur. In 1972 Parker and co-workers showed a significant decrease in serum complement components after CPB but with the assay methods available at the time it was impossible to know whether this occurred by activation or denaturation [26]. In 1977 Craddock and co-workers proposed a mechanism for pulmonary dysfunction in patients undergoing haemodialysis and nylon fibre leucophoresis [27]. They found that during these procedures there was a selective loss of neutrophils and monocytes from the systemic circulation with trapping in the lungs. Both of these cells have membrane binding sites for the complement anaphylatoxin C5a and the cellophane dialysis membrane had chemical

similarities to certain substances such as bacterial lipopolysaccharide which activates complement by the alternative pathway.

In an animal model for Adult Respiratory Distress Syndrome, Hohn gave plasma with complement activated by zymosan to rabbits. This resulted in profound systemic neutropenia followed by hypoxaemia, tachypnoea and haemorrhagic pulmonary oedema [28]. Electron microscopy showed degranulated neutrophils marginated in the pulmonary capillaries. These, it is suggested, release their lysosomal granules releasing cathepsins and proteases such as collagenase and elastase. Oxygen-free radicals are generated in the process and collectively these factors result in damage to the membranes of the alveolar capillary barrier. This results in increased permeability to fluid and protein and gives a histological picture indistinguishable from that seen after CPB.

In 1981 Hammerschmidt and co-workers claimed that the pulmonary sequestration of neutrophils and monocytes that occurs in patients during CPB was direct evidence for complement activation. Their data for total complement levels and C3 and C5 fragments however did not support their hypothesis or clarify the relationship between complement activation and peripheral leucopenia [29]. Cooper had previously shown that infusion of activated complement into sheep produced a rise in serum concentrations of prostaglandin metabolites (thromboxane B2) and that treatment with prostaglandin inhibitors (indomethacin or sulphinpyrazone) eliminated both the prostaglandin rise and pulmonary dysfunction without altering the peripheral leucopenia [30]. Thus a positive link between complement, white cells, CPB and pulmonary dysfunction remained in doubt pending direct evidence of complement anaphylatoxin release. Hugli and Chenoweth succeeded in isolating the anaphylatoxins in C3a and C5a, determined their amino acid sequence and synthesized their molecules thus establishing a method for immunoassay [31]. Chenoweth, working in conjunction with the cardiac surgeons at the University of Alabama, demonstrated that C3a appeared rapidly in the plasma at the onset of CPB and accumulated in increasing quantity until the end of perfusion when levels fall due to tissue binding. C5a is so rapidly bound to white cell membranes that a significant rise in the serum could not be detected. Neutrophil trapping in the pulmonary circulation was confirmed by white cell counts in right and left arterial blood. This was the first demonstration that these powerful mediators of the acute inflammatory response were liberated during extracorporeal circulation [32]. Subsequently, it was shown that nylon and many other allegedly biocompatible materials from the bypass circuit caused temperature dependent C3a release in vitro as did the reaction between heparin and protamine. Merely bubbling oxygen continuously through plasma, a process simulating bubble oxygenation, was sufficient to cause anaphylatoxin release. Westaby, Kirklin and others went on to show that C3a levels in patients after bypass could be related to cardiac, pulmonary, renal and coagulation disturbances lending support to the systemic inflammatory response hypothesis [33].

Using the C3a assay Van Oeveren and others showed that both bubble and membrane oxygenators cause similar degrees of complement activation via the alternative pathway [34]. The pattern of C3a release during the surgical procedure is temperature related. At the onset of perfusion when blood contacts the foreign materials at normothermia C3a is rapidly released into the circulation where its half life is short (20 – 30 min). As the temperature of the perfusate is reduced to 27 °C the levels of C3a fall and remain at a steady level until the re-warming phase when presumably production is accelerated and peak levels are obtained, (Westaby, unpublished data). However, this late phase of C3a generation also coincides with aortic cross clamp removal and re-perfusion of the ischaemic heart and pulmonary vasculature. Wildevuur and others postulated that the oxygenator was not the only source of complement activation [35]. Their suggestion was that material dependent accelerated production of C3a towards the end of bypass should not occur in membrane oxygenators when the C3b binding sites on the artificial surface must be saturated. They showed that administration of corticosteroids before bypass could prevent the rise in C3a and leucocyte sequestration after release of the aortic cross clamp although C3a was generated *equally* in treated and untreated patients before that time. C4a plasma levels as a marker for complement activation by the classical pathway were not significantly altered in either group of patients except that C4a was increased in the group without corticosteroids following release of the aortic cross clamp. This suggests that ischaemia in the myocardium and pulmonary vasculature during aortic cross clamping (with little or no pulmonary and myocardial blood flow) induces complement activation by the classical pathway which may be moderated by pre-treatment with corticosteroids. Plasminogen activator produced by the ischaemic pulmonary epithelium may be the stimulus for this.

White cells, lysosomal enzymes and oxygen free radicals

Though the anaphylatoxins C3a and C5a are spasmogens and can themselves increase membrane permeability it is likely that they are only the stimulus for

subsequent events. C5a in particular promotes leucocyte chemotaxis and release from the bone marrow [36]. The lung plays an important role in leucocyte kinetics because the marginated cells that it contains can be mobilised from the pulmonary to the general circulation in times of stress. Quiroga and others studied leucocyte kinetics during CPB in patients undergoing coronary artery surgery and compared hypothermia with normothermia throughout the procedure [36]. Both polymorphonuclear leucocytes and lymphocytes were taken up by the lungs as pulmonary blood flow was lowered at the beginning of the procedure. This effect has been noted experimentally in dogs and occurs in the absence of complement activation following a decrease in pulmonary blood flow to 10% of normal. In normothermia, peripheral white blood cell counts doubled during the procedure owing to a release of polymorphonuclear leucocytes and their precursors from the bone marrow. This increase was prevented by hypothermia but reappeared quickly when the body temperature was restored to 37 °C. This pattern of response parallels the previously described C3a anaphylatoxin levels.

Recent studies by Westaby, Fleming and Royston in coronary patients with moderate hypothermic perfusion (27 °C) have further characterised white cell changes and particularly white cell trapping after aortic cross clamp release [37]. Transpulmonary white cell counts show a modest progressive rise in polymorphonuclear leucocytes in both central venous and left atrial blood until cross clamp removal and coincident systemic rewarming to 37 °C. At this time, as the heart begins to eject and blood flow is restored to the ischaemic myocardium and pulmonary vasculature, the central venous white count rises and the left atrial count falls. It has been calculated that as many as 50% of the circulating polymorphonuclear leucocytes are selectively trapped in the pulmonary capillaries whereas lymphocytes are unaffected. Notably, polymorphs have membrane binding sites for C5a anaphylatoxin whereas lymphocytes do not. An aggregate of 30 – 40 polymorphs produces a significant embolus of 80 – 90 μm in diameter.

Using the thiobarbituric acid reaction to measure products of lipid peroxidation as an index of free radical activity they found peak levels at the time of neutrophil trapping following cross clamp removal [38]. This implies a direct relationship between white cell trapping and free radical peroxidation of membrane lipids. However, reperfusion after ischaemia in itself generates free radicals via the xanthine dehydrogenase/oxidase mechanism and may therefore contribute to lipid peroxidation at this time. Certainly the complement anaphylatoxin, white cell, free radical mechanism of membrane damage is an attractive explanation of the observed findings after CPB. Though the lung has been studied predominantly because of ease of access during CPB, it is likely that white cell trapping also occurs in less accessible organs such as the liver and kidneys.

Degenerating neutrophils and those stimulated to the 'killing phase' by C5a release their lysosomal contents. These proteolytic enzymes were implicated in the pulmonary damage of CPB as long ago as 1966 when Replogle suggested that pre-treatment with corticosteroids may have a protective effect [39]. Interestingly, Van Oeveren has recently demonstrated that pre-treatment with corticosteroids can moderate white cell trapping by the lungs after cross clamp release [35]. Branthwaite and others demonstrated lysosomal enzyme release from the lungs in patients during CPB [40] and Bolanowski suggested that prostaglandin E1 might have a more protective effect than corticosteroids [41]. Prostaglandin E1 had previously been shown to maintain the integrity of lysosomes from the spleen, kidney and pancreas of rats. This action is mediated by increasing levels of cyclic 3'5 adenosine monophosphate (cyclic AMP) and it is known that cyclic AMP inhibits release of lysosomal enzymes from polymorphonuclear leucocytes. More recently a new assay for elastase as a marker for neutrophil activation has caused renewed interest. Havel and coworkers have demonstrated a striking peak in this enzyme 5 min after removal of the aortic cross clamp which coincides with a significant decrease in the antiproteases antitrypsin and macroglobulin [42]. These findings tie in very well with the timing of white cell trapping and lipid peroxidation. Cochrane and others have demonstrated the presence of neutrophil elastase and evidence of oxidative activity in bronchoalveolar lavage fluid of patients with adult respiratory distress syndrome, a condition which appears similar to the post perfusion pulmonary dysfunction both morphologically and functionally [43]. In addition Zaslow and others have shown that human neutrophil elastase does not bind to $Alpha_1$-protease inhibitor that has been exposed to activated human neutrophils [44]. The natural antidote to elastase release is therefore ineffective during CPB.

Platelets are also trapped in the lung after cross clamp removal and greatly increase the white cell induced endothelial damage by producing serotonin. This amplifies the endothelial cytotoxicity of the cell by increasing its adhesion to endothelium. Serotonin is produced in the brain and packaged in platelets. It is interesting that the adult respiratory distress syndrome occurs in stress induced situations and demonstrates considerable patient variability in its manifestations. Serotonin provides one theoretical link between stress and the severity of the pulmonary lesion

in trauma victims, (Craddock, personal communication). Endorphins such as enkephalin block the serotonin effect and increase endogenous prostacyclin production thereby inhibiting platelet and PMN adherence.

The net effect of this perfusion injury is an increase in membrane permeability, washout and decreased production of surfactant by type II pneumocytes and inflammatory oedema. For the patient this causes decreased pulmonary compliance, increased work of breathing and excess secreations. The great majority tolerate and compensate well for this. Intubation and ventilation for 12 – 18 h post-operatively is still regarded as part of normal post-operative convalescence despite stable haemodynamics. Those who cannot tolerate a decreased compliance (the very young, the elderly and the severely debilitated) or those with an exaggerated response require prolonged ventilatory support with the risk of pulmonary infection and a respiratory death.

Therapeutic implications

There are numerous opportunities for intervention in this complex series of events. Firstly, it is known that materials such as nylon activate the complement system more avidly than others and may be replaced by less potent polymers both in the oxygenators and cardiotomy reservoir. Passivation of the foreign surfaces by albumen or other plasma proteins may further limit their complement activating ability. Eventually membranes may be developed which are locally active for instance by the efforts to immobilise heparin and PGE_1 on polyhydroxyethyl methacrylate. Continuous bubbling causes complement activation and may therefore perpetuate this in bubble oxygenators even when the surfaces are coated with protein. Membrane oxygenators may therefore have an advantage in this respect if corticosteroids can eliminate non-material related complement activation during reperfusion of the ischaemic heart and lungs.

Temperature manipulation by prolongation of the hypothermic phase used in most cardiac surgery may prove beneficial. Beginning perfusion with the perfusate precooled to 20 °C should minimize the effects of the initial normothermic exposure of blood to foreign surfaces, though accelerated anaphylatoxin generation is inevitable during re-warming. Paradoxically, hypothermia reduces the ability of the lung to eradicate bradykinin during CPB though the significance of this is unknown.

When C3a and C5a are formed in human plasma they are inactivated by carboxypeptidase N an enzyme which selectively removes only the carboxyterminal arginyl residue from each molecule. With continued production of anaphylatoxin, clearance becomes less efficient as levels of carboxypeptidase decrease. Pretreatment with a synthetic derivative of this enzyme could theoretically moderate the effects of anaphylatoxin production.

Inhibition of granulocyte adherence may prevent leucoemboli or margination of neutrophils activated by C5a. MacGregor and co-workers inhibited granulocyte adherence with ethanol, prednisone and aspirin [45]. As stated, PGE_1 prevented intravascular pulmonary leucocyte aggregation during CPB to a greater extent than methyl prednisolone [41]. PGE_1 diminishes platelet and granulocyte adherence to endothelium, fibronectin and plastics and also inhibits PMN superoxide production. Cytochalasin B is said to prevent damage by complement activated PMN's despite similar amounts of oxgen radicals produced. Drugs such as methysergide and imiprimine block the serotonin platelet effect and have the potential to reduce the amplifying effect on PMN endothelial cytotoxicity. Aspirin similarly has this effect but its profound effect on bleeding time prohibits its use during CPB.

Cyclo-oxygenase inhibitors that effectively inhibit platelet aggregation by inhibiting prostaglandin synthesis have very little effect on neutrophil aggregation though both are initially triggered by translocation of calcium across the membrane.

Although steroid pre-treatment does not seem to protect against complement activation in the clinical situation, steroids have been said to moderate the pulmonary insult of shock and trauma by reducing the increase in pulmonary vascular resistance, reducing platelet entrapment, enhancing fibronectin activity, stabilising lysosomal membranes and decreasing the inflammatory response leading to maturation of alveolar type II pneumocytes which in turn causes increased surfactant activity [46 – 48]. Elevation of lysosomal enzyme fractions during CPB can be moderated by corticosteroids. However, past experience has shown little objective benefit with the use of pharmacological doses of steroids (30 mg/kg body wt of methyl prednisolone) and the circulatory and subcellular metabolic effects are modest and short lived. The most promising future development in this field is the development by genetic engineering of potent specific protease inhibitors such as Eglin from the leech which blocks the effects of elastase and Cathepsin G.

Under hypoxic conditions in the bypassed lung proteases are released which are at least in part responsible for conversion of Xanthine dehydrogenase to oxidase thus establishing a substrate for free radical generation at reperfusion. Of possible therapeutic interest is the ability of the protease inhibitor aprotinin to prevent this conversion and to protect against other lysosomal enzymes liberated from sequestrated

neutrophils [49]. Interference with the damaging effects of lipid peroxidation by free radical species may come about with the use of agents that function intra- or extracellularly to reinforce the endogenous antioxidant protective systems (superoxide, dismutase, catalase, glutathione, vitamins E and C, cysteamine). Exogenous superoxide dismutase preparations have shown experimental efficacy and suggest that superoxide dismutase or bovine catalase could offer some degree of protection from oxygen radical attack by neutrophils especially if less rapidly cleared enzyme preparations with longer plasma half lives become available [50]. However, they are less effective in blocking free radicals produced by complement stimulated white cells than with the xanthine oxidase system. Free radical scavengers such as mannitol and chlorpromazine are available for clinical use but have not specifically been tested in this context.

Clearly in the future a great many changes will occur in the conduct of CPB, and the possibilities for pharmacological protection against damaging effects will increase. Currently for those patients at greatest risk a combination of agents including corticosteroids, PGE_1, a non-steroidal anti-inflammatory agent such as Ibrufen and naturally occurring free radical scavengers such as methionine and vitamin C might be expected to offer protection if given prophylactically.

It is important not to become complacent about our 'acceptable' results in 1986, but to aim for negligible bypass related mortality and morbidity in the future.

References

1. Dodrill FD (1958) The effects of total body perfusion on the lungs. In: Allen JG (ed) Extracorporeal circulation. Springfield, Thomas, p 327
2. Allardyce DB, Yoshida SH, Ashmore PG (1966) The importance of microembolism in the pathogenesis of organ dysfunction caused by prolonged use of the pump-oxygenator. J Thorac Cardiovasc Surg 52:706
3. Kirklin JW (1980) Open heart surgery at the Mayo Clinic; the 25the Anniversary. Mayo Clin Proc 55:339
4. Kirklin JK, Blackstone EH, Kirklin JW, McKay R, Pacifico AD (1981) Intracardiac surgery in infants under three months. Incremental risk factors for hospital mortality. Am J Cardiol 48:500
5. Downs JJ, Nicodemus HF, Pierce WS, Waldhausen JA (1970) Acute respiratory failure in infants following cardiovascular surgery. J Thorac Cardiovasc Surg 59:21
6. Westaby S (1983) Complement and the damaging effects of cardiopulmonary bypass. Thorax 38:321
7. Bachmann F, McKenna R, Cole ER, Najafi H (1975) The haemostatic mechanism after open heart surgery. I. Studies in plasma coagulation factors and fibrinolysis in 512 patients after extracorporeal circulation. J Thorac Cardiovasc Surg 70:76
8. McKenna R, Bachmann F, Whittaker B, Gilson JR, Weinberg M (1975) The haemostatic mechanism after open heart surgery. II. Frequency of abnormal platelet function during and after extracorporeal circulation. J Thorac Cardiovasc Surg 70:298
9. Abel RM, Buckley MJ, Austen WG, Barnett GO, Beck CH, Fischer JE (1976) Aetiology, incidence and prognosis of renal failure following cardiac operations. J Thorac Cardiovasc Surg 71:323
10. Abel RM, Wick J, Beck CH, Buckley MJ, Austen WG (1974) Renal failure following open heart operations. Arch Surg 108:175
11. Lillehei CW, Cohen M, Warden HE, Zeigler NR, Varco RL (1955) The results of direct vision closure of ventricular septal defects in eight patients by means of controlled cross circulation. Surg Gynecol Obstet 10:447
12. Reed CC, Ramagnoli I, Taylor DE, Clark DF (1974) Particulate matter in bubble oxygenators. J Thorac Cardiovasc Surg 68:971
13. Lee WH, Krumbhaar D, Fomkalsrud EW. Schjeide OA, Maloney JV (1961) Denaturation of plasma proteins as a cause of morbidity and death after intracardiac operations. Surgery 50:29
14. Livelli FD, Johnson RA, McEnany MT (1978) Unexplained in-hospital fever following cardiac surgery. Circulation 968
15. Anderson NB, Ghia J (1970) Pulmonary function, cardiac status and post operative course in relation to cardiopulmonary bypass. J Thorac Cardiovasc Surg 59:474
16. Kouchoukos NT, Karp RB (1981) Functional disturbances following extracorporeal circulatory support in cardiac surgery. In: Ionescu MI (ed) Techniques in extracorporeal circulation. Butterworths, London, p 297
17. Snashall PD, Weidner WJ, Staub NC (1977) Extravascular lung water after extracellular fluid volume expansion in dogs. J Appl Physiol 42:624
18. Boldt J, Bormann B, Kling D, Hoge R, Hempelmann G (1985) The influence of cardiopulmonary bypass on lung water content. In: Hagl S, Klovekorn WP, Mayr N, Sebening F (eds) Thirty years of extracorporeal circulation. Deutsches Herzzentrum München, p 127
19. Royston D, Catley DM, Higgenbottam T, Wallwork J, Minty BD (1986) Changes in alveolar capillary barrier function associated with cardiopulmonary bypass. Ann Thorac Surg
20. Wilson JW (1974) The pulmonary cellular and subcellular alterations of extracorporeal circulation. Surg Clin North Am 54:1204
21. Ratliff NB, Young WG, Hackel DB, Mikat E, Wilson JW (1973) Pulmonary injury secondary to extracorporeal circulation. J Thorac Cardiovasc Surg 65:425
22. Connell RS, Page US, Barley TD, Bigelow JC, Webb MC (1973) The effect on pulmonary ultra structure of Dacron wool filtration during cardiopulmonary bypass. Ann Thorac Surg 15:217
23. Morgan TE (1971) Pulmonary surfactant. N Engl J Med 284:1185
24. Barratt-Boyes BG, Simpson M, Neutze JM (1971) Intracardiac surgery in neonates and infants using deep hypothermia with surface cooling and limited cardiopulmonary bypass. Circulation 43 and 44 (Suppl II):25
25. Ruddy S, Gigli I, Austen KF (1972) The complement system of man. N Engl J Med 287:489
26. Parker DJ, Cantrell JW, Karp RB, Stroud RM, Digerness SB (1972) Changes in serum complement and immunoglobulins following cardiopulmonary bypass. Surgery 71:824
27. Craddock PR, Fehr J, Dalmasso AP, Brigham KL, Jacobs HS (1977) Haemodialysis leukopenia. Pulmonary vascular leukostasis resulting from complement activation by dialyser cellophane membranes. J Clin Invest 59:879
28. Hohn DC, Meyers AJ, Gherini ST, Beckman A, Markison RE,

Churg AM (1980) Production of acute pulmonary injury by leucocytes and activated complement. Surgery 88:48
29. Hammerschmidt DE, Stroncek DF, Bowers TK, Lammi-Keefe CJ, Kurth DM, Ozalins M, Nicoloff DM, Lillehei RC, Craddock PR, Jacobs HS (1981) Complement activation and neutropenia occurring during cardiopulmonary bypass. J Thorac Cardiovasc Surg 81:370
30. Fountain SW, Martin BA, Musclow CE, Cooper JD (1980) Pulmonary leukostasis and its relationship to pulmonary dysfunction in sheep and rabbits. Circ Res 46:175
31. Hugli TE, Chenoweth DE (1981) Biologically active peptides of complement. Techniques and significance of C3a and C5a measurements. In: Nakamura RM, Dito WR, Tucker ES (eds) Future perspectives in clinical laboratory immunoassays. Alan R Liss, New York, p 443
32. Chenoweth DE, Cooper SW, Hugli TE, Stewart R, Blackstone EH, Kirklin JW (1981) Complement activation during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxins. N Engl J Med 304:497
33. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Pacifico AD, Chenoweth DE (1983) Complement and the damaging effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg 86:845
34. Van Oeveren W, Kazatchkine MD, Descamps-Latscha B, Maillet F, Fischer E, Carpertier A, Wildevuur CRH (1985) Deleterious effects of cardiopulmonary bypass. A prospective study of bubble versus membrane oxygenation. J Thorac Cardiovasc Surg 89:888
35. Van Oeveren W, Yan-Ji J, Eysman L, Jansen D, Wildevuur CRH (1966) Corticosteroids inhibit material-independent complement activation during cardiopulmonary bypass. Submitted to J Thorac Cardiovasc Surg
36. Quiroga MM, Miyagishima R, Haendschen LC, Glovsky M, Martin BA, Hogg JC (1985) The effect of body temperature on leucocyte kinetics during cardiopulmonary bypass. J Thorac Cardiovasc Surg 90:91
37. Royston D, Fleming JS, Desai JB, Westaby S, Taylor KM (1986) Increased production of peroxidation products associated with cardiac surgery. Evidence for free radical generation. J Thorac Cardiovasc Surg 91:759
38. Westaby S, Fleming JS, Royston D, Taylor KM (1984) Evidence for generations of free radical species during cardiopulmonary bypass in man. In: Hagl S, Klovekorn W, Mayr N, Sebening F (eds) Thirty years of extracorporeal circulation. Deutsches Herzzentrum München, p 389
39. Replogle RL, Gazzaniga AB, Gross RE (1966) Use of corticosteroids during cardiopulmonary bypass. Possible lysosomal stabilisation. Circulation 33 and 34 [Suppl I]:86
40. Gnanadurai TV, Branthwaite MA, Colbeck JF, Wellman E (1978) Lysosomal enzyme release from the lungs after cardiopulmonary bypass. Anaesthesia 33:227
41. Bolanowski PJ, Bauer J, Machiedo G, Neville WE (1977) Prostaglandin influence on pulmonary intravascular leucocytic aggregation during cardiopulmonary bypass. J Thorac Cardiovasc Surg 73:221
42. Havel M, Duma S, Graninger W, Moritz A, Fasol R, Zilla P (1984) Release of granulocyte elastase during cardiopulmonary bypass. In: Interactions of cells with natural and foreign surfaces. Abstracts of symposium. Institute of Basic Medical Sciences, Royal College of Surgeons, p 42
43. Cochrane CG, Spragg RG, Devak SD, Cohen AB, McGuire WW (1983) The presence of neutrophil elastase and evidence of oxidant activity in bronchoalveolar lavage fluid of patients with the adult respiratory distress syndrome. Am Rev Respir Dis 127:525
44. Zaslow MC, Clark RA, Stone PJ, Calore JD, Snider GL, Franzblau C (1983) Human neutrophil elastase does not bind to alpha$_1$-protease inhibitors that has been exposed to activated human neutrophils. Am Rev Respir Dis 128:434
45. MacGreger R, Spanuolo P, Lefner A (1974) Inhibition of granulocyte adherence by ethanol, prednisolone and aspirin measured with an assay system. N Engl J Med 291:642
46. Sibbald WJ, Anderson RR, Reid B, Holliday RL, Driedger AA (1981) Alveolar-capillary permeability in human septic adult respiratory distress syndrome. Chest 79:133
47. Goldstein IM, Roos D, Weissman G, Kaplan HB (1976) Influence of corticosteroids on human polymorphonuclear leucocyte function in vitro, reduction of lysosomal enzyme release and superoxide production. Inflammation 1:305
48. Sladen A (1976) Methylprednisolone – pharmacological doses in shock lung syndrome. J Thorac Cardiovasc Surg 71:800
49. Fritz H, Winderer G (1983) Biochemistry and applications of aprotinin, the Kallikretin inhibitor from bovine agents. Arzneimittelforsch 33:479
50. McCord JM, Wong K, Stokes SH, Retrone WF, English D (1980) Superoxide and inflammation: a mechanism for the anti-oxidant activity of superoxide dismutase. Acta Physiol Scand [Suppl] 429:25

Mr. S. Westaby FRCS
Department of Cardiothoracic Surgery
The Middlesex Hospital
Mortimer Street
London W1N 8AA
UK