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REVIEW ARTICLE

Non-cardiogenic Pulmonary Oedema in Vascular Surgery

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Non-cardiogenic pulmonary oedema, an early manifestation of the adult respiratory disease syndrome, is a serious complication following major vascular surgery. Hypovolaemia, ischaemia-reperfusion injury, massive blood transfusion, transient sepsis and transient endotoxaemia are insults responsible for initiating the process in vascular surgical patients. Free radicals, cytokines and humoral factors released secondary to the above insults activate neutrophils and facilitate their interaction with the endothelium. Activated neutrophils marginate through the endothelium where they are responsible for tissue injury by the release of free-radicals and proteases. The lungs are a large reservoir of neutrophils and bear a significant part of the injury. Conventional therapy includes treating the underlying condition and providing respiratory support. A better understanding of the pathophysiology of this process has led to new experimental treatment options. Novel therapeutic interventions have included the use of compounds to scavenge free radicals, anti-cytokine antibodies, extracorporeal lung support, nitric oxide and artificial surfactant therapy. The multifactorial nature of this process makes it unlikely that a single "magic bullet" will solve this problem. It is more likely that a combination of preventative, prophylactic and therapeutic modalities may reduce the mortality of this condition.

Introduction

Pulmonary complications contribute significantly to the postoperative morbidity and mortality data reported following major vascular surgery.[1] Pre-existing respiratory disease, inadequate postoperative epidural analgesia and inadequate postoperative physiotherapy leading to pulmonary atelectasis and infection have traditionally been held responsible for postoperative respiratory complications.[2,3] Events that occur during vascular surgical procedures can trigger a set of events that lead to acute pulmonary injury.[4,5] This in turn has been reported to lead to pulmonary oedema of non-cardiogenic origin progressing to the adult respiratory distress syndrome and respiratory failure.[6,7] A large multicentre prospective study found that respiratory failure complicates 8% of patients undergoing non-ruptured abdominal aortic surgery[8] and 47% of patients undergoing surgery for a ruptured abdominal aortic aneurysm.[9]

The importance of non-cardiogenic pulmonary oedema is that it may be the first clinical sign of a larger process, the systemic inflammatory response syndrome, which when left unchecked leads to multiple organ failure.[10,11] Due to intensive preoperative optimisation of cardiac function, some recent series have reported multiple organ failure as the leading cause of death following abdominal aortic aneurysm surgery, relegating death due to cardiac complications to second place.[12,13]

In this review the pathophysiology of factors contributing to non-cardiogenic pulmonary oedema and therapeutic manoeuvres that may limit this disease process will be discussed.

The Adult Respiratory Distress Syndrome

The adult respiratory distress syndrome (ARDS) was first described during the Vietnam War in victims surviving multiple trauma, shock and burns.[14] It is now known that there are many aetiological factors

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Table 1. Aetiology of acute lung injury.

Direct lung injury:
Aspiration pneumonia
Infectious pneumonia
Other pneumonitis: oxygen, smoke inhalation, radiation
Direct Trauma: lung contusion, penetrating chest injury
Near drowning
Fat embolism
Distant injury:
Sepsis syndromes: inflammation, necrosis, infection
Ischaemia reperfusion injury
Multiple trauma
Burns
Shock or hypoperfusion
Acute pancreatitis
Blood transfusion related acute lung injury

for ARDS, which can be conveniently classified into direct lung injury and distant lung injury (Table 1).

The clinical features of ARDS are of progressive hypoxia leading to respiratory failure. The initial features usually present about 16–24 h after the initiating insult with little more than hypoxia, tachypnoea and tachycardia. Clinically there are minimal signs of pulmonary oedema on auscultation and the chest X-ray is normal. Over the next 24 h the patient will develop increasing dyspnoea and hypoxia with mild clinical signs such as inspiratory rhonchi. The chest X-ray is usually non-specific at this stage, showing diffuse alveolar shadows which are often attributed to infection or fluid overload. The syndrome progresses to a picture of severe hypoxia, reduced lung compliance secondary to alveolar collapse, inflammatory infiltration of the lungs, oedema, surfactant depletion, increased airway resistance and superimposed infection, making ventilation difficult. Chest X-ray at this stage will show the typical "ground-glass" appearance in both lungs.[15–19]

Established ARDS has a mortality rate of about 60%. Advanced age, pre-existing lung disease, sepsis or the development of additional organ system failures increases the mortality rate to 70–90%.[14,19,20]

Post-mortem studies show that early pathological changes in ARDS include pulmonary neutrophil sequestration and intravascular fibrin-platelet aggregates. Subsequent injury to the alveolar-capillary barrier leads to progressive lung inflammation and pulmonary oedema. Increased numbers of neutrophils marginate along the endothelial surfaces and migrate into the interstitium and the alveoli.[18,21,22]

The latter stages of ARDS are associated with inflammatory cell and fibroblast infiltration, pneumocyte proliferation, gradual obliteration of the pulmonary microvasculature and some fibrosis. This explains the progressive decrease in lung compliance. Progressive pathological features include alveolar collapse due to infiltration with blood, oedema fluid and inflammatory infiltrate. Small airway collapse leads to bronchial obstruction and provides an ideal environment for superimposed infection. At this stage lung surfactant levels are found to be depleted.[17,18,22] Late features include eventual interstitial fibrosis.[23]

Pathophysiology of Acute Lung Injury in Vascular Surgery

The aetiological factors responsible for acute lung injury in vascular surgical procedures include aortic cross-clamping and the consequent ischaemia-reperfusion injury, hypovolaemia, shock, transient sepsis, transient endotoxaemia and massive blood transfusion.[4,5,7,22,24–28]

The processes that cause the lung damage are initiated in areas quite remote from the lung (Fig. 1). During reperfusion, free radicals are formed at the sites subjected to the ischaemic insult (most commonly the lower limbs). The reperfusion process floods these free radicals into the systemic circulation where they can initiate damage either directly by themselves, indirectly by activating neutrophils and the endothelium or by providing a stimulus for the further production of cytokines. A similar process occurs in the hypoperfused regions during shock. The process of resuscitation washes the toxic metabolites into the systemic circulation where they initiate lung damage. The metabolites involved will be discussed shortly, but it is important to note that most of these mediators encourage neutrophil–endothelial interaction; leading to migration of neutrophils into tissues where damage is caused by the degranulation of these cells.[26,29,30] The pulmonary vascular bed is known to store between 50–60% of the total circulating neutrophil pool, causing major sequestration of neutrophils into pulmonary tissue making the lungs a major site of tissue damage (Fig. 1).[31] Neutrophils cause pulmonary damage by releasing toxic metabolites including proteases and free radicals.[32] The factors responsible for acute lung injury can be conveniently grouped into four types for descriptive purposes: free radicals, neutrophils, factors derived from the endothelium and humoral factors.

Free radicals

Ischaemia-reperfusion injury is an inevitable consequence of recovery from acute limb ischaemia and

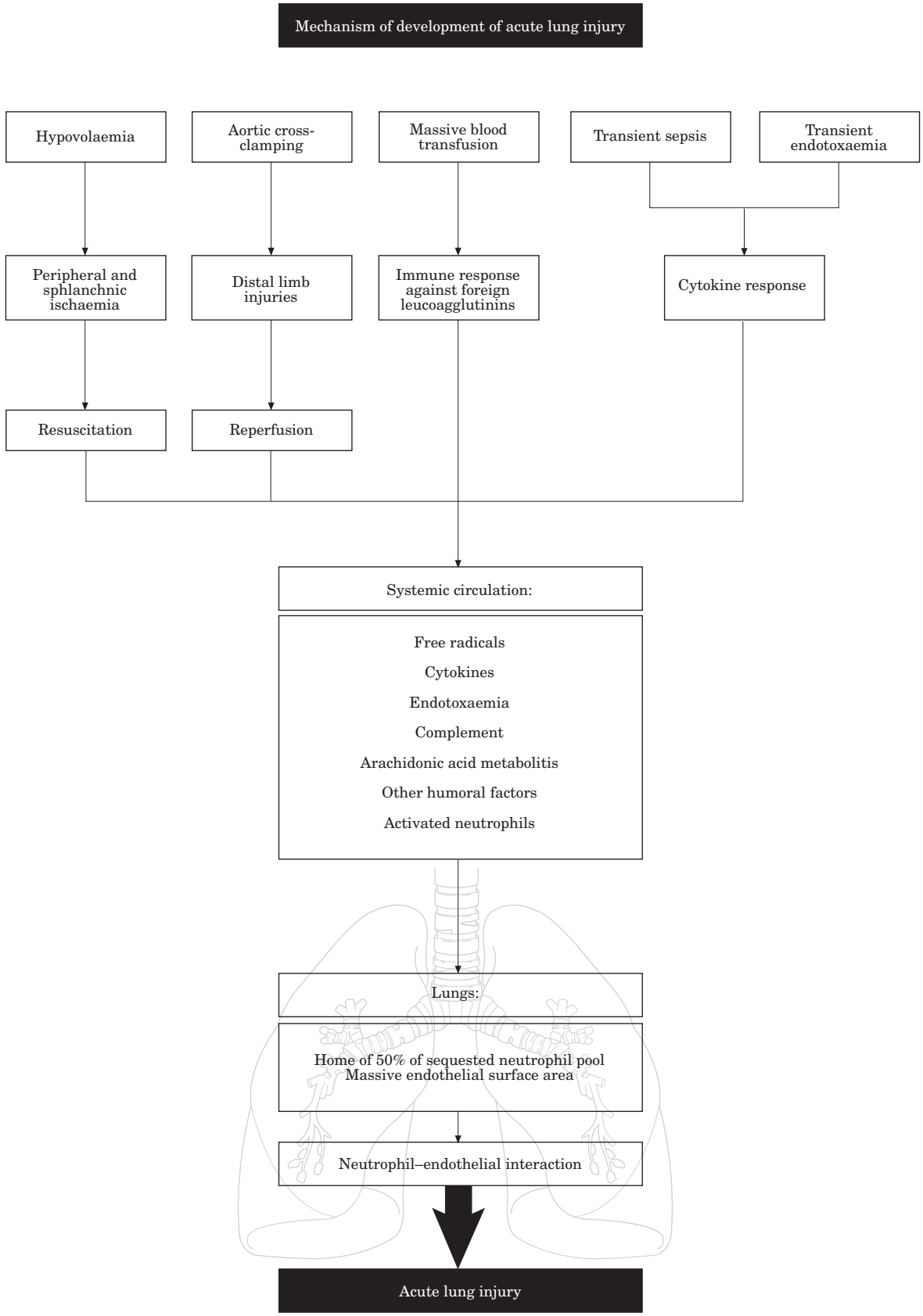

Fig 1. Mechanism of development of acute lung injury.

shock. Furthermore, aortic cross-clamping is inevitable during open aortic surgery subjecting the lower torso to ischaemia-reperfusion. Free radicals are responsible for much of the systemic damage induced by reperfusion injury.[33]

A free radical is any unstable molecule containing one or more unpaired electrons; making them chemically highly reactive.[34] The main free radicals responsible for tissue damage in biological systems include the superoxide ion (O_2^-) and the hydroxyl ion (OH^-).[35] Also of note are nitric oxide (NO) both itself and by its reaction with O_2^- to form OH^- and the peroxynitrite anion ($ONOO^-$).[36]

The xanthine dehydrogenase/oxidase system is responsible for the majority of free radicals formed during ischaemia-reperfusion. Xanthine dehydrogenase is a naturally occurring enzyme which under normal circumstances converts hypoxanthine (a breakdown product of ATP metabolism) to uric acid.[38,39] During ischaemia, xanthine dehydrogenase is converted to an isoform of this enzyme called xanthine oxidase (XO) by calcium activated proteases in ischaemic tissue.[39,40] Xanthine oxidase catalyses the conversion of hypoxanthine to xanthine in the presence of molecular oxygen, releasing the superoxide (O_2^-) free radical in the process.[35,41]

During ischaemia, tissue levels of xanthine oxidase accumulate. Furthermore, depletion of ATP causes a rise in tissue levels of hypoxanthine. Reperfusion of ischaemic tissue with oxygenated blood introduces the second substrate for XO activity in abundance – namely molecular oxygen. This causes a massive burst in XO activity, leading to the release of large quantities of the superoxide free radical.[35,42]

Superoxide dismutase is a naturally occurring enzyme which scavenges superoxide ions in physiological circumstances. Superoxide dismutase converts the superoxide ion to hydrogen peroxide.[43–45]

$$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

During pathological states of ischaemia-reperfusion, ferric iron is reduced to the ferrous state by O_2. Ferrous iron can donate an electron to hydrogen peroxide, which dismutates to form the hydroxyl radical (OH^-). The hydroxyl radical (OH^-) is reputed to be the most reactive of free radicals in biological systems.[46]

Free radicals cause tissue damage by lipid peroxidation of cell membranes; a process initiated by the removal of a hydrogen atom from a methylene group positioned between two unsaturated bonds of a lipid molecule. The result is a carbon centred lipid free radical which in the presence of oxygen results in further lipid degeneration and consequent cell membrane damage. Proteins and DNA are also at risk from structural damage by free radicals.[33,47]

Superoxide free radicals react with endothelial cells to promote the formation of inflammatory mediators, the expression of endothelial leucocyte adhesion molecules and inactivate nitric oxide formed by the endothelium, thus encouraging the neutrophil–endothelial interaction required for pulmonary leucosequestration.[48,49]

Leucocytes

Neutrophils are the first line of defence against invading organisms; however, during processes of prolonged stimulation this potent armamentarium is directed against the host. Neutrophils cause tissue damage by two mechanisms; the generation of free radicals and the release of proteolytic degenerative enzymes.

The enzyme reduced nicotinamide adenine dinucleotide oxidase transfers electrons from reduced nicotinamide adenine dinucleotide (NADPH) to molecular oxygen generating superoxide ions:[50,51]

$$2O_2 + NADPH \rightarrow 2O^{2-} + NADP^+ + H^+$$

Superoxide dismutase is present in neutrophils, hence hydrogen peroxide is produced as described before. In the neutrophil, the enzyme myeloperoxidase catalyses the formation of hypochlorous acid:[52]

$$H_2O_2 + Cl^- + H^+ \rightarrow HOCl + H_2O$$

Hypochlorous acid is a potent oxidising and chlorinating agent. It reacts rapidly with primary amines to produce N-chloramines, which are also potent oxidising agents. The cytotoxic effects of these oxidising agents are mediated through the oxidation of sulphyl groups, inactivation of haem proteins and cytochrome, and the degradation of protein.[42] Nitric oxide (NO) is also produced by activated neutrophils; when released together with superoxide ions the effects are likely to be locally cytotoxic, as NO reacts with superoxide to form the highly injurious peroxinitrite and hydroxyl radicals.[36,53]

The neutrophil's cytosolic granules contain a potent cocktail of proteolytic enzymes including elastase, gelatinase and collagenase. These enzymes cause severe damage to the pulmonary tissue and basement membrane.[54]

During normal physiological states up to 60% of

the total neutrophil pool is stored in the pulmonary vasculature. Unlike the systemic vasculature, where most of the cellular components marginate and interact with the endothelium in the post-capillary venules, neutrophils are found mainly in the low pressure pulmonary capillary bed.[55] Neutrophils must change from their loosely associated state in the pulmonary vasculature to interact with the pulmonary endothelium before they can initiate acute lung damage. Numerous stimuli including the proinflammatory cytokines (tumor necrosis factor α, interleukin-1, interleukin-8), complement, platelet-activating factor and free radicals initiate neutrophil–endothelial interaction by initiating the endothelium to express a group of endothelial leucocyte adhesion proteins and activate neutrophils to express complementary glycoprotein adhesion receptors. Superoxide also inactivates endothelial nitric oxide – an endogenous anti-adhesion molecule. As a consequence, neutrophils adhere to the first activated endothelium they encounter. The lungs are a major site of neutrophil pooling and may undergo significant tissue damage leading to acute lung injury.[56]

The neutrophil–endothelium interaction occurs in two stages. Endothelial cells activated by proinflammatory cytokines express a group of leucocyte adhesion proteins called selectins: namely, endothelial leucocyte adhesion molecule (ELAM or E-selectin), intercellular adhesion molecule (ICAM or CD54) and granule membrane protein 140 (GMP140 or P-selectin).[57–59]

All neutrophils express a group of proteins on their surface called lectin adhesion molecules (LECAM). The LECAM receptor readily bonds to ELAM, hence a large number of neutrophils are arrested from the circulating pool and bind to endothelium.[26] Inflammatory mediators produced locally by the inflamed endothelium now stimulate the bound neutrophils to express a group of glycoproteins on their cell surface called integrins. The important integrins expressed by activated neutrophils include CD11b and CD18.[60] The CD11b and CD18 receptors firmly attach themselves to ICAM, while LECAM receptors are rapidly shed. The integrin–selectin adhesion then allows unopposed migration of the neutrophil between endothelial cells.[61] Activated neutrophils can now cause cellular damage by initiating the respiratory burst and releasing free radicals and protease into this environment. Activated neutrophils also block the microcirculation hindering normal blood flow.[62]

Circulating monocytes are recruited into areas of inflammation in a similar manner to neutrophils. Monocyte diapedesis across the endothelium requires the endothelial expression of monocyte chemoattractant protein (MCP). Once in the intima, monocytes secrete chemotactic cytokines and MCP in large quantities, attracting further inflammatory cells to the region.[63] Some of these monocytes transform into pulmonary tissue macrophages with phagocytic properties and the capability of releasing free radicals and proteases. Once activated in the pulmonary tissue these cells play a central response in processing foreign antigens and presenting them to lymphocytes. They are also a major source of chemotactic factors including tumour necrosis factor, interleukins and arachidonic acid metabolites.[64,65] The cells derived from monocytes play a greater role in the latter stages of acute lung injury during the development of ARDS.

The endothelium

In addition to the expression of leucocyte adhesion molecules which are vital to pulmonary leucosequestration as described above, the endothelium produces a wide range of molecules and humoral factors which regulate the development of acute lung injury. These substances include arachidonic acid metabolites, nitric oxide, cytokines and other humoral factors.

The enzyme phospholipase A2 releases arachidonic acid from vascular endothelial cell membranes. Arachidonic acid is further metabolised to prostacyclins and thromboxane by the cyclo-oxygenase pathway. Leukotrienes are formed by the action of lipoxygenase on arachidonic acid.[66]

Prostacyclin causes vascular smooth muscle relaxation and reduces platelet aggregation. It may provide some protection during the development of acute lung injury, but endogenous prostacyclin is unstable and its synthesis is impaired by smoking, diabetes, atherosclerosis and increasing age.[33] Increased thromboxane A2 (TA2) levels have been documented following aortic cross-clamping, ischaemia reperfusion injury and shock.[7,67,68] TA2 is a potent vasoconstrictor, stimulates platelet aggregation and is a powerful chemoattractant, facilitating neutrophil migration across activated endothelium.[66,69] Leukotriene B4 (LB4) is another important arachidonic acid metabolite involved in the genesis of acute lung injury. LB4 binds to specific receptors on neutrophils and activates neutrophils to increase expression of surface CD18, encouraging neutrophil-endothelial interaction and the generation of free radicals and proteases.[70]

Nitric oxide (NO) is an important endogenous mediator involved in the control of normal vascular tone. Local stimuli to the endothelium including shear stress and local hormones promote the liberation of NO as

a by-product of the conversion of L-arginine to L-citrulline by vascular endothelial constitutive nitric oxide synthase. The net result of endogenous NO on the vascular endothelium includes relaxation of vascular smooth muscle and inhibition of neutrophil and platelet adhesion to the endothelium. In the lung NO also mediates bronchodilatation via a local non-cholinergic non-adrenergic pathway.[53]

NO metabolism is profoundly affected during pathological states. Inflammation, sepsis and other conditions that promote increased serum levels of endotoxin and cytokines can lead to an increased production of endothelial nitric oxide by the up-regulation of a second enzyme – inducible nitric oxide synthase (iNOS).[71] Following induction, iNOS is active for >20 h and produces NO at over a thousand-fold concentrations compared to cNOS.[72]

One of the most important effects of NO is vasodilation. This effect may reduce the "no-reflow" phenomenon commonly seen in ischaemia-reperfusion injury, whereby the microvascular circulation exhibits capillary spasm and plugging with activated leucocytes. The vasodilatory action of increased NO synthesis may be a contributory factor to the hypotension seen during septic shock.[73]

However, superoxide produced during ischaemia reperfusion is known to inactivate endogenous NO, hence promoting endothelial–neutrophil interaction.[49] Superoxide also reacts with NO to form the peroxinitrite free radical ($ONOO^-$), a free radical in its own right as well as a precursor of the hydroxyl anion.[36]

During chronic hypoxic states, including the events following acute lung injury, pulmonary NO synthesis and release is suppressed, accounting for some of the pulmonary hypertension and bronchoconstriction seen. The rationale for the administration of inhaled NO in established ARDS is that it can cause local pulmonary vasodilation and bronchodilatation and thus improve oxygenation. Furthermore, any NO absorbed into the bloodstream will be immediately inactivated by haemoglobin and other proteins and hence will not be able to exert its systemic effects.[74–77]

Endothelin is the most potent vasoconstrictor known. It is a family of peptides synthesised in response to hypoxia, thrombin, noradrenaline and transforming growth factor beta. Endothelin causes vasoconstriction and encourages neutrophil–endothelial interactions. During physiological states the balance between the antagonist effects of endothelin and nitric oxide regulate vascular tone. This can be severely deranged, causing vascular constriction and plugging of vessels during pathological states.[78,79]

Platelet activating factor (PAF) is a phospholipid derivative produced by endothelial cells in response to injury. PAF is an important mediator of ischaemia-reperfusion induced leucocyte chemotaxis. Within the microcirculation, PAF encourages platelet aggregation, thrombus formation and alters microvascular permeability.[80]

The endothelium is also capable of releasing complement and cytokines. These humoral factors are also produced in significant quantities by leucocytes and other cells in the reticuloendothelial system.

Humoral factors

Aortic cross-clamping, ischaemia-reperfusion injury, haemorrhage and transient sepsis are all potent stimuli for the formation of a host of inflammatory humoral factors including complement and cytokines. Activation of the complement cascade is indicated by an increase in serum levels of the active peptides C3a and C5a as seen following major vascular surgical procedures.[81,82] These anaphylatoxins cause increased capillary permeabiliy and vasodilation. Increased complement activity also enhances neutrophil chemotaxis, upregulates neutrophil CD18 receptor expression and promotes neutrophil free radical production and degranulation.[83]

Cytokines are a group of low molecular weight proteins produced by cells involved in the inflammatory response. These molecules are responsible for coordination and communication in the immune and inflammatory systems and include chemokines, interleukins, growth factors and interferons. These factors have a transient action which is tightly regulated and are very active at low concentrations. They have multiple effects that overlap between factors and are involved in the growth and differentiation of various cell types as well as the activation of cells to express specific protein synthesis. The important factors in the development of ARDS and multiple organ failure in vascular patients include tumor necrosis factor-α (TNF-α), interleukin- 1 (IL1), interleukin-6 (IL-6) and interleukin-8 (IL-8).[84–86]

TNF-α is produced by many cells in the reticuloendothelial system including monocytes, pulmonary macrophages and hepatic Kupffer cells in response to ischaemia reperfusion, shock, transient endotoxaemia and sepsis.[11,87] TNF-α acts by binding to specific receptors on a wide variety of cells. The actions of TNF-α include the release of neutrophils from the bone marrow, neutrophil activation and migration into the pulmonary endothelium by the upregulation of adhesion molecules and neutrophil free radical and protease production. TNF also stimulates the endothelium

to synthesise PAF.[88,,89] TNF-α promotes the differentiation and activation of monocytes and macrophages, stimulates the formation of acute phase proteins, activates the complement cascade and induces the release of IL-1.[90,91]

Interleukin-1 is released in parallel or in response to TNF. It stimulates the formation of granulocytes and macrophages by inducing granulocyte/macrophage colony stimulating factor. IL-1 also increases endothelial–leucocyte interactions by up-regulating adhesion molecules and potentiates leucocyte-mediated damage by stimulating free radical and lysozyme release.[11,89] Interleukin-6 and IL-8 act synergistically with TNF-α and IL-1 to modulate leucocyte-mediated lung injury.[92] Interleukin-6 has been demonstrated to facilitate endothelial–neutrophil adhesion.[93] Interleukin-8 is produced by endothelial cells and is a potent leucocyte chemoattractant.[94]

Transforming growth factor β is an angiogenic peptide that inhibits neutrophil–endothelial adhesion, deactivates macrophages and opposes the effects of TNF-α. Future work may find therapeutic use for this factor.[95]

In addition to pro-inflammatory cytokines, cytokines with predominantly anti-inflammatory actions have been identified. Interleukin-10 (IL-10) is one such cytokine that can inhibit TNF-α, IL-1 and IL-6. These anti-inflammatory cytokines are involved in tightly controlling the systemic inflammatory response.[96]

Endotoxaemia and breakdown of the intestinal barrier

Studies have demonstrated that elective and emergency abdominal aortic aneurysm repair are associated with an increase in intestinal permeability.[97] Colonic ischaemia is an uncommon but lethal complication of abdominal aortic aneurysm repair.[98] The splanchnic vasculature is the last to recover following resuscitation from shock. All the above situations result in a transient period of endotoxaemia.[99,100]

Endotoxin is a potent stimulus for the generation of TNF-α and the proinflammatory interleukins. This in turn leads to neutrophil mediated lung injury. It has been argued by some that transient endotoxaemia is a powerful contributor to multiple organ failure after major surgery, although others doubt its overall significance.[101,102].

The intestinal barrier function depends on the normal microbiological flora of the gut, enteric secretions, peristalsis, the endothelium and gut-derived immune cells. These factors are markedly changed in critically ill patients. Prolonged starvation or administration of total parenteral nutrition leads to villous atrophy, billiary stasis and compromised gut immune function. This in turn makes the host vulnerable to attack from the potentially pathogenic gut flora.[103]

Blood transfusion

The complications of blood transfusion include fluid overload, transfusion related infection and anaphylactic reactions. Donor blood can activate host defence mechanisms by the introduction of foreign antigens in donor leucocytes and platelets. The effects of a mild transfusion related reaction are often manifested clinically as urticaria and pyrexia. Activation of the host defence mechanism leads to upregulation of cytokines and neutrophil-induced acute lung injury.[24]

The systemic inflammatory response syndrome

The systemic inflammatory response syndrome (SIRS) is defined by the presence of two or more of the following conditions: (a) temperature greater than 38 °C or less than 36 °C; (b) heart rate greater than 90 beats per minute; (c) respiratory rate greater than 20 breaths per minute or an arterial partial pressure of carbon dioxide lower than 4.3 kPa and (d) white blood cell count greater than 12 000 or less than 4000 cells per mm^3 or with more than 10% immature forms.[104] Non-cardiogenic pulmonary oedema is often an early clinical manifestation of SIRS. Many of these patients will go on to develop multiple organ failure.[11]

The pathogenesis of SIRS has been described by Bone to develop in three stages. The first stage is a normal response to an insult which may be any of those seen in vascular surgical procedures including shock, haemorrhage, aortic cross-clamping, ischaemia reperfusion injury, endotoxaemia, sepsis or blood transfusion. The response to this insult is the production of cytokines such that the host's inflammatory response is evoked to repair tissue damage by recruitment of cells in the reticuloendothelial system.[105]

In the second stage of the development of the SIRS small quantities of cytokines released into the circulation recruit neutrophils and macrophages, and initiate an acute-phase response. This response is tightly controlled and is gradually downregulated (by anti-inflammatory cytokines) while the initiating insult resolves.

If the initial insult persists, SIRS may develop and results in a large concentration of cytokines. The first

clinical signs will be a temperature, tachycardia and non-cardiogenic pulmonary oedema. The sustained activation of the reticuloendothelial system results in the loss of microcirculatory integrity and eventual multiple organ failure.[105]

Prevention of Acute Lung injury in Vascular Surgery

The key to preventing acute lung injury is to minimise factors that evoke a strong systemic inflammatory response. In vascular surgical practice this would include the prevention of massive haemorrhage, shock and the consequent need for large blood transfusions. Decreasing blood transfusion requirements may help limit the host's response to foreign antigens. Preoperative blood donation combined with haemodilution and the salvage and retransfusion of autologous blood have been demonstrated as safe means of decreasing blood transfusion requirements in aortic surgery.[106,107]

Aortic endovascular techniques avoid the need for aortic cross-clamping and the consequent lower torso ischaemia-reperfusion injury. There is evidence to suggest that endovascular aortic surgery evokes a smaller systemic inflammatory response.[108]

A degree of transient endotoxaemia is associated with aortic cross-clamping and haemorrhage but ischaemic colitis is an uncommon complication of abdominal aortic reconstruction. The latter condition is often diagnosed late, and consequent endotoxaemia usually leads to death from multiple organ failure.[109] A high index of suspicion seems to be the most useful method of diagnosing and treating ischaemic colitis early, the use of intrarectal pH monitoring being a useful adjunct to early diagnosis.[110]

The prophylactic use of agents to minimise ischaemia reperfusion damage may be one method of limiting acute lung injury. Free radical scavengers are agents that react with reactive oxygen species and neutralise them. Endogenous free radical scavengers exist – namely superoxide dismutase. Many exogenous compounds including dimethylsulphoxide, dimethylthiourea and histidine have been demonstrated to inactivate free radicals *in vitro* or in animal models;[33,111] however, mannitol remains the most reliable and proven exogenous free radical scavenger in clinical practice.[112] Allopurinol is an inhibitor of the enzyme xanthine oxidase, and there are data to support its use at a low dose to prevent the effects of ischaemia reperfusion injury.[113]

Antioxidants are compounds that stop lipid peroxidation and limit damage, e.g. vitamin E, captopril, propranolol, calcium antagonists and nafazatarom, but none of these compounds have been found to be useful in a clinical setting.[111]

Much of the research on the prophylactic prevention of leucocyte–endothelial interaction has been directed towards blocking adhesion molecules by antibodies directed against them. Although these techniques are effective in animal models, human studies have been disappointing.

Systemic administration of heparin before the application of vascular clamps is common in clinical practice. Heparin inactivates proteins released from ischaemic tissues, prevents endothelial damage, neutralises lysosomal cationic proteins released by leucocytes, limits the activation of complement and promotes the formation of prostacyclin. Heparin also has antiplatelet and anti-inflammatory properties. These beneficial effects of heparin are due to its large size and negative charge, which prevents neutrophil–endothelial interactions.[114–116]

Hetastarch, dextran and mannitol have also been shown to protect against ischaemia-reperfusion induced lung injury in animal models by preventing endothelial–leucocyte interactions.[117–119]

Future Treatment Options Following the Development of ARDS

Current therapy for patients who develop postoperative respiratory failure remains mainly supportive. Supplementary oxygen and positive pressure mechanical ventilation are critical to the maintenance of adequate gas exchange. Prolonged oxygenation produces lung injury identical to that seen in other causes of ARDS; furthermore, significant lung damage and barotrauma are complications of high transalveolar pressures. Details of mechanical ventilation are outside the scope of this article, but some of the methods used to provide adequate gas exchange while limiting inhaled oxygen consumption (FIo_2) and ventilatory pressures include providing a small tidal volume and optimal positive end–expiratory pressure.[21,91,120–122]

Other non-conventional methods of ventilatory support include high-frequency ventilation using breathing frequencies up to 300 breaths per min,[123] and tracheal gas insufflation using a small continuous flow of fresh gas from the distal endotracheal tube during exhalation.[124,125]

Optimum fluid balance, inotropic support and the support of failing organ systems are specific to individual patients. Diagnosis of nosocomial pneumonia

in these patients can be difficult and invasive techniques including bronchoscopy may be required to improve diagnostic sensitivity.[126]

Selective decontamination of the digestive tract has been shown to reduce the rate of respiratory complications in critically ill patients. The upper gastrointestinal tract is often colonised by endogenous human gut flora in critically ill patients because of duodenal reflux, bowel stasis and mucosal atrophy in these patients. Aspiration of upper gastrointestinal secretions leads to respiratory complications and selective gut decontamination may be protective.[127] There is debate about the value of early enteral feeding following major surgery. Enteral feeding stimulates hepatic function and splanchnic blood flow, and may protect against acalculous cholecystitis and preserve gut mucosal barrier and immunological function.[128]

Exogenous inhaled NO produces local vasodilation and reverses pulmonary vasoconstriction due to hypoxaemia in ventilated parts of the lung. In patients with ARDS, inhaling NO increases the arterial oxygen tensions and decreases pulmonary hypertension,[56,129] and the benefits of this technique in infants and adults with ARDS have been reported.[130–133] Reported complications of inhaled NO include changes in platelet function, worsening of left ventricular failure and rebound hypoxia on withdrawal. Levels of methaemoglobin, NO and NO_2 have to be adequately monitored.[134] Preliminary results of one large multicentred study has failed to demonstrate any improved mortality.[135] Inhaled NO as therapy for ARDS has to be used with caution till the full results of large clinical trials in Europe and the USA are published.[136]

Extracorporeal membrane oxygenation (ECMO) is a technique developed from cardiopulmonary bypass, where an extracorporeal circuit provides oxygenation while the injured lungs are allowed to recover. However, a multicentre trial in the 1970s failed to show any advantage of this technique over traditional ventilation.[137] Despite improvements in the technology, a recent trial has also failed to show any significant benefits.[138]

Monoclonal antibodies directed against components of endotoxin have reduced mortality of patients with Gram-negative sepsis[139,140] but the results have not been reproducible in a more recent study.[141] Studies attempting to antagonise the effect of IL-1 have failed to demonstrate any clinical benefit.[142] Prophylactic haemofiltration has been performed as a method of decreasing blood endotoxin and cytokine levels in patients at high risk of developing ARDS and multiorgan failure.[143]

Antagonism of thromboxane (a vasoconstrictor and promoter of platelet aggregation) alone with ketokonazole has been explored clinically with encouraging results.[144] Prostaglandin E1 (PGE1) is a vasodilator that has been shown to improve gas exchange and attenuate the release of free-radicals and cytotoxic enzymes from activated granulocytes.[145] Recent pilot trials have demonstrated that inhaled PGE1 improved oxygenation and decreased venous admixture without affecting systemic haemodynamic variables. The results were comparable to NO and this new form of treatment warrants a large multicentre randomised clinical trial.[146,147]

Surfactant depletion during acute lung injury is responsible for alveolar collapse and decreased lung compliance in progressive ARDS. Surfactant also has important anti-inflammatory functions, including the inhibition of TNF-α, IL-1 and IL-6 production by alveolar macrophages. The use of both natural and artificial surfactant therapy is being studied, but, despite encouraging results in the use of this therapy in neonatal acute lung injury, no benefit has been demonstrated in adults.[148,149]

Other treatment strategies include the use of antioxidants to alleviate free-radical induced damage. Mannitol has been shown to reduce ischaemia-reperfusion induced end organ damage in human trials.[112] Newer compounds being tested include N-acetylcysteine and an exogenous form of aerosol superoxide-dismutase which may act locally in the lung.[91,150] A recent consensus committee document stated that steroids are not recommended in most cases of ARDS.[151]

Ischaemic preconditioning is a physical method of limiting ischaemia-reperfusion damage. This phenomenon is based on the observation that a series of short ischaemic episodes followed by reperfusion confers a degree of protection against further ischaemia-reperfusion injury.[152] The mechanism of ischaemic preconditioning is not fully understood, but the formation of adenosine during the ischaemic phase is thought to be involved, and administration of exogenase adenosine has some protective effects in experimental work. A further group of proteins called heat-shock proteins have been implicated in ischaemic preconditioning, although the mechanism by which these stress proteins exert their protective effect has not been fully elucidated.[153,154]

Conclusions

Aggressive preoperative control of cardiac function together with better resuscitation and intensive-care

therapy continues to decrease the postoperative cardiac mortality following major vascular surgery. However, many patients still develop the systemic inflammatory response syndrome and eventually succumb to the consequences of acute respiratory distress syndrome or multiple organ failure. Patients with ruptured AAA are particularly at risk.

Despite the massive research directed towards the pathology of ARDS, it is unlikely that a "magic bullet" will be found due to the multifactorial aetiology of the condition. A realistic hope may be the development of a combination of treatment modalities that may reduce the mortality of this condition.

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