Mediators of multiple organ failure

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Abstract. Multiple Organ Failure (MOF) has largely been attributed to bacterial sepsis, though conclusive evidence of an essential role for bacteria and/or their endotoxins is still lacking. On the other hand, MOF and the clinical syndrome of sepsis may be aseptically induced in germ-free animals. This paper reviews the evidence that excessive activation of endogenous humoral mediators and inflammatory cells may cause this highly lethal syndrome.

Key words: Multiple organ failure – ARDS – Sepsis – Complement – Elastase – Neopterin

The adult respiratory distress syndrome (ARDS) with subsequent sequential failure of multiple organ functions (MOF) and the clinical syndrome of sepsis, still carries a mortality of 60%. Since the first authors to describe ARDS noticed that these patients subsequently die of sepsis [1], there is a consensus that bacterial overgrowth is the cause of this highly lethal syndrome. However the evidence for such a causal relationship is poor: (1) MOF also develops in patients with primarily non-bacterial problems such as severe pancreatitis severe trauma before bacterial invasion is obvious, (2) no single study could reliably demonstrate positive blood cultures or elevated levels of circulating endotoxin preceding MOF [2–8], (3) no clinical, biochemical or morphological differences could be found between patients with the "clinical" sepsis syndrome (no bacteremia, no focus) and patients with the "classical" sepsis syndrome (bacteremia, septic focus) [2, 8], (4) the drainage of pus [9], administration of antibiotics or decontamination of the gastro-intestinal tract does not necessarily prevent or suppress MOF [10], (5) a MOF-like syndrome may be induced aseptically in germ-free rats by intraperitoneal inoculation of zymosan [11].

Evidence is slowly gathering that excessively activated endogenous inflammatory compounds and cells may be themselves responsible for structural damage and functional deterioration in remote vital organ systems. In this article a brief and necessarily incomplete summary is given of the – possibly harmful – biological effects of several inflammatory mediators, products and cells, and of the available evidence of their activity in patients with ARDS, and the subsequent syndrome of MOF and "clinical" sepsis.

Inflammation

The sequence of events in inflammation, e.g. after local tissue trauma begins with the local activation of the different cascade systems (complement, coagulation, fibrinolytic and kinin-kallikrein), generating mediators from circulating proteins. Some of these mediators (anaphylatoxins: C3a, C5a) have strong chemotactic effects on circulating inflammatory cells (granulocytes, monocytes), activate these cells to produce proteolytic enzymes and toxic oxygen radicals, and have effects on local mast-cells which release histamine. In the next phase, cellular mediators have an important role. The wound granulocytes and macrophages release systemic signals (e.g. GM-CSF, PGE-2, TNF, IL-1, IL-6) to adapt the organism to the local requirements of the local problem. The wound therefore has been aptly called an endocrine organ [12].

Though inflammation is intended to be a local process, it is obvious that in severely ill patients with signs of generalised "sepsis" a systemic activation or spill-over of inflammatory products and mediators may be expected. From experience, clinicians are well aware of the "risk-factors" for such an event, and the actual incidence of ARDS, MOF and sepsis in some prospective studies of patients at risk was up to 80%. The "abnormal" systemic presence of any inflammatory mediator would then be a Marker of the MOF-syndrome, and the change from normal should correlate with the severity of MOF. However, if these compounds are themselves causing damage to otherwise healthy tissues and their specific functions, their detection in abnormal amounts in the systemic circulation should predict MOF. At present only a very few Predictor studies are available.

Mediators from circulating proteins

In general, mediators derived from circulating proteins are products of a cascade of activation steps that sequentially convert proenzymes to their active counterpart. The endogenous mediator activity is modulated by inhibitors, inactivators, the half-life of the mediator, the responsiveness of the target organ and − in some cases − the cellular destruction of the mediator [13]. In order to cause MOF, these mediators should (1) be found in abnormal concentrations in the blood prior to MOF, with a high specificity and sensitivity (2) induce hemodynamic, biochemical and morphologiocal alterations ressembling MOF if administrated experimentally.

From the available data on the different cascade systems in (predicting) MOF, only the complement system has been well-studied (for non-complement mediators, see [6, 13−15]). The complement system is activated by antigen-antibody complexes, endotoxin, enzymes released from PMNs and macrophages, plasmin, platelet products, products of virus-infected cells and by exposed collagen. The biologically active substances are C3a and C5a and the cytolytic terminal complement complex C5-C9. C3a and C5a have strong chemotactic properties, activate PMNs, release enzymes from PMNs, and release histamine from mast cells. In this respect C5a is 100 times more potent than histamine and 1000 times more than C3a [16]. C5a also increases capillary permeability in collaboration with PGE_2 [17], and induces IL-1 and TNF production.

Experimental infusion of autologous zymosan-activated plasma in rabbits has been shown to induce tachypnoea, leucopenia, granulocyte aggregation and sequestration in the lung, liver, kidney and heart [18] resembling the early morphological changes in ARDS and MOF [19]. These alterations, however, are not severe and are largely reversible. Only with an additional stimulus such as hypoxia, could severe MOF-like morphological changes be induced in the experiment [18]. On the other hand, in complement depleted or complement deficient experimental animals, the pulmonary response to inflammatory stimuli is significantly diminished [20, 21]. Low plasma-levels of the complement compounds C3 and C4 have been found in MOF-patients [14, 22] indicating complement activation, but possibly also decreased synthesis. Elevated plasma-levels of C3a have been found prior to the development of ARDS by several authors [23−25]. C5a assessed with radio-immuno assay could not be correlated or was not predictive of MOF in several studies [14, 23−25], while C5a-like activity assessed by aggregometry was predictive [26, 27]. In most studies however, elevated levels of the anaphylatoxins could only be found at an early stage of disease. Also C5a has a short half-life as it is rapidly internalised by PMNs. Possibly the most suitable compound for assessment in the complement cascade is the stable split-product of C3, C3d [14, 27], which also was predictive of MOF [14].

Inflammatory cells and their products

PMNs

Though ARDS has been described in neutropenic patients, the direct and indirect involvement of PMNs in ARDS and MOF has by now clearly been established [18, 19, 28−30]. Studying the numbers and functions of circulating PMNs in MOF however, may not be relevant [31], since biologically active PMNs aggregate and stick to endothelial cells, and peripheral blood PMNs may not be representative of the activated population. Also the peripheral white-cell count only reflects the balance between bone marrow synthesis and de-margination of PMNs, and margination and breakdown of PMNs. Most information about PMN-dynamics would be obtained by PMN-turnover, but we have no method to assess this rate of turnover.

At the site of inflammation, PMNs release numerous active substances, such as proteolytic enzymes (elastase, collagenase, cathepsin G) and toxic oxygen-radicals, vasoactive substances (PAF-acether, leukotrienes, PGE_2) and wound-hormones (MAF, GM-CSF). Actually it might be more appropriate to measure these substances as an index of PMN activity. Presently, the measurement of most of these substances (leukotrienes, eicosanoids, PAF, MAF, GM-CSF, oxygen radicals and lipid-peroxidation products) in clinical patients is either impossible, impractical (LTB4 only in bile, PAF by bio-assay) or has barely been done. Increasing data are available on elastase, products of the cyclo-oxygenase pathway and free radicals.

Elastase. Elastase is a serine-protease that is capable of degrading elastin, collagen III and IV, proteoglycans, fibronectin, clotting factors and fibrinolytic factors, complement factors C3 and C5, immunoglobulins, proteinase-inhibitors and transport proteins such as ferritin. Elastase is essential for PMN-mediated endothelial injury [32, 33]. The fact that 60% of plasma-proteins are proteinase-inhibitors illustrates that the body needs a thorough protection against proteinases.

Experimental administration of elastase results in elevated pulmonary vascular resistance, decreased cardiac output, pulmonary leucostasis, DIC, and increased venous admixture of oxygen [34]. Elastase can be monitored in clinical patients as the complex with its inhibitor α1-antiprotease by an ELISA-method, and more recently by a rapid IMAC-test [35]. All studies available have shown a positive relation between elastase and severity of ARDS, sepsis or MOF in several conditions such as major trauma, burns and peritonitis [6, 8, 14, 35−41]. A few studies found elastase to predict MOF [14, 35, 36]. One study could demonstrate that the rise in EVLW in trauma patients occured subsequent to a prior rise in elastase and C3a [41].

The present evidence suggests an important role for elastase as a marker of PMN-activity, and possibly as a predictor of ARDS and MOF, though specific plasma levels have yet to be set for this predictive value.

Cyclooxygenase pathway products. Whenever cell-membranes are damaged, the arachidonic acid cascade is activated. Especially activated PMNs, but also macrophages, platelets and endothelial cells may produce large amounts of the most potent vasodilator prostacyclin and vasoconstrictor thromboxane. The action of prostacyclin and thromboxane is primarily expressed in the local environ-

ment. Their half-lifes are short, while a systemic spill-over is completely cleared from the blood during the first passage through the pulmonary capillaries. The early pulmonary hypertension in ARDS and sepsis is due to the action of thromboxane and abolished by cyclo-oxygenase inhibitors. Cyclo-oxygenase inhibitors are however, unable to block the sequence of events leading to full-blown ARDS and MOF. Also in ARDS, the pulmonary clearance of prostacyclin is incomplete, leading to systemic vasodilation, possibly contributing to the hyperdynamic circulation and supply-dependent oxygen consumption in these patients.

Though several clinical studies have shown elevated plasma-levels of these compounds in ARDS and MOF, the available data are conflicting and the alterations found are not predictive (for review see [42]). Experimental administration of these compounds induces only part of the (circulatory) alterations seen in ARDS and MOF.

Presently the prostaglandins of the E series have been studied in ARDS and sepsis because of their immuno-modulatory and anti-inflammatory capacities. PGE_1 is also a pulmonary vasodilator. Administration of PGE_1 in the animal experiment could not prevent ARDS [43], and administration to patients with ARDS has not improved survival [44]. PGE_2 — a product of PMNs, macrophages and various pulmonary cells, and also released whenever increased cell-membrane arachidonic acid release occurs — down-regulates the aspecific immune system by stimulating the suppressor cell line and suppressing T-cell proliferation. PGE_2 depresses PMN function, is anti-inflammatory on macrophages, turns down TNF and IL-1 production. PGE_2 thus may initiate the events leading to immunodepression.

In vitro, adding PGE_2 strongly increases vascular permeability induced by C5a and PMNs [17]. Hitherto, no studies are available on the effects of experimental administration of PGE_2 in relation to MOF. In clincal patients, elevated PGE_2 levels correlated with sepsis [45].

Free radicals. Free radicals are unstable atoms, with an unpaired electron in their outer electron-ring. Free radicals of oxygen are formed by activated phagocytes (oxydative burst), by most cell-types upon reoxygenation after hypoxia through activation of xanthine-oxidase, and as a by-product of activation of the arachidonic acid cascade. Free radicals induce the process of lipid-peroxidation (e.g. leading to cell-membrane damage with deleterious influx of calcium into the cell), to inactivation of enzymes (e.g. of α1-antiprotease leading to uncontrolled activity of free elastase) and of detoxifying agents, e.g. glutathion (for review see [46]). Through all these effects, free radicals are potent inflammatory agents. Experimental administration of (agents inducing) free radicals closely mimicks ARDS [47] and MOF [48].

Human PMNs have been demonstrated to produce much higher concentrations of free radicals in response to inflammatory stimuli than bovine, ovine or porcine PMN [49], possibly explaining why the human race is so sensitive to inflammatory stimuli.

A major problem in determining the involvement of free radicals in patients prone to ARDS and MOF is the difficulty of demonstrating their presence or effects in vivo, as free radicals have an extremely short half-life and are rapidly inactivated by ubiquitous free-radical scavengers. One way to circumvent this problem, is to measure stable end-products of lipid-peroxidation, such as malondialdehyde (MDA). MDA is elevated in plasma after cardio-pulmonary bypass [50], and in pulmonary tissue of trauma-patients dying of ARDS and sepsis [51]. The MDA-method, however, is subject to criticism, and more studies are urgently needed utilising newer methods such as lipofuscin and hydroxy-nonenal.

Macrophages

Macrophages are present in most tissues such as the brain (glia-cells), the lung (alveolar macrophages), the kidney (mesangial cells), the peritoneum, the spleen. The hepatic Kuppfer cells comprise 70% of the total population of fixed tissue macrophages. Circulating monocytes are attracted to the site of inflammation, and differentiate locally to macrophages. Macrophages are activated directly by C5a, and by a score of signals from PMNs such as GM-CSF, low molecular MSF and PMN -IL1 like activity (for review see [52]).

Macrophages that have been treated with activated complement or interferon are referred to as "inflammatory" or "elicited" macrophages, as these stimuli are insufficient to completely activate them. Treatment with more potent stimuli such as LPS stimulates macrophages fully, and these are referred to as "activated" macrophages [52]. Apparently it takes several days after triggering to develop the full inflammatory reaction of macrophages.

Upon stimulation, macrophages may release some 53 different classes of secretory products [53], of whom some are pro-inflammatory (proteolytic enzymes, oxygen radicals, IL-1, TNF), others anti-inflammatory (PGE_2), immunosuppressive (IL-2) or pro-coagulatory. Again, most of these mediators are difficult to monitor clinically. One solution may be to measure neopterin, a stable end-product of macrophage activity.

Interleukin-1. IL-1 (endogenous pyrogen) induces fever and hypermetabolism, stimulates fibroblasts and endothelial cells to produce GM-CSF and PGE_2, enhances PGE_2 synthesis in the hypothalamus, increases skeletal muscle proteolysis, has a priming effect on macrophages, is important for maintaining the gut-mucosal barrier and turns on the liver synthesis of acute phase proteins (for review see [53, 54]).

Experimental administration in rabbits results in hypotension, decreased peripheral resistance, increased heart rate and cardiac output, leukopenia and thrombocytopenia [55]. IL-1 thus possesses the ability to induce hemodynamic and hematologic changes typical of sepsis and to duplicate a series of events in MOF, but at present no easy "in-vivo" assay is available.

Tumor necrosis factor. TNF (cachectin) induces fever, hyperglycemia and hyperkalemia, increases PMN-aggregation, phagocytosis, adherence to endothelial cells and oxygen radical formation, blocks the proliferation of endothelial cells and enhances the killing of endothelial

cells by PMN, decreases the synthesis of key-enzymes, induces IL-1 production. TNF-activity is suppressed by PGE$_2$ (for review see [53, 56]). Experimental administration of TNF results in fever, diarrhea, tachypnea, hypotension, metabolic acidosis, elevated lactate levels, lethargy, ARDS-like changes in the lung, hemorrhagic necrosis of the kidneys and adrenals, and finally death [56–58]. These alterations closely ressemble the effects of endotoxin administration in man [59].

At present, only a limited number of studies are available on TNF in relation to sepsis and MOF [7, 60]. TNF plasma levels correlated well with lactate levels, severity of illness and mortality [7, 60]. No correlations were found with positive blood cultures [61], endotoxin-levels [7], nor with subsequent ARDS, shock or mortality [61].

Neopterin. Though in itself inactive, neopterin (a pteridine related to dopamine) [62] may offer a practical way of monitoring macrophage activity in patients with or at risk of ARDS, sepsis and MOF. γ-Interferon and LPS cause the release from macrophages of neopterin in a dose dependent way [63]. Plasma-neopterin levels in endotoxemia correlated well with the clinical signs of sepsis but not with the plasma level of endotoxin [64]. In clinical studies, plasma-levels of neopterin correlated well with the severity of ARDS, MOF and sepsis and could accurately predict non-survivors several days before the event [8, 65, 66].

Mast cells

Mast cells are present in virtually every tissue. Their perivascular location permits exposure to circulating factors as well as rapid release of mediators into the circulation. The mast cell mediator content of human skin alone exceeds that needed to cause cardiac arrest and proteolysis by 2000-fold [13]. The content of heparin in these cells is estimated to be 100-fold greater than that needed to cause full anticoagulation [13]. PAF from mast cells may activate platelets. Despite their ubiquitous presence and strong inflammatory properties, presently no method is available to monitor the activity of mast cells in ARDS and MOF.

Summary and conclusion

Summarizing the inflammatory capacities of the three types of inflammatory cells — PMNs, macrophages and mast cells — each type seems able to induce a lethal whole body reaction. This whole body inflammation has hitherto largely escaped our attention, as in clinical studies inappropriate methods have been used such as counting peripheral leucocytes, and as monitoring key-mediators (IL-I, TNF, PGE$_1$, leukotrienes) and key-cells (activated PMNs, macrophages and mast cells) hitherto was impossible. Presently a new set of methods is available, allowing a closer look at this whole body inflammation, such as elastase (monitoring PMN activity), neopterin (monitoring macrophage activity) and hopefully clinically practicable methods to monitor cytokines as well as endotoxin-levels. Only after such comprehensive studies

have been performed, might it be concluded that — as in the experimental animal — sepsis and MOF may not necessarily be caused by bacteria or their endotoxins, but by an untoward autodestructive and self-sustaining activation of our own inflammatory cells.

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