Introduction

The host response to invasive infection and other forms of tissue injury has been termed the systemic inflammatory response syndrome (SIRS) [1]. A complex defence network, with inflammatory cytokines as key mediators, is generated to restore normal homeostasis [2]. In certain circumstances, excessive amounts of pro-inflammatory mediators are released into the systemic circulation, leading to a generalized and uncontrolled host response that overwhelms the natural inhibitors of inflammation [3]. In recent years, several new therapies designed to block the synthesis or toxicity of a particular component of the SIRS cascade have been proposed, including anti-tumour necrosis factor α (TNFα) monoclonal antibodies, interleukin-1 (IL-1) receptor antagonists and platelet activating factor (PAF) antagonists. Although preliminary studies were encouraging, large multi-centre trials have failed to show clear benefits [4, 5].

Numerous reasons have been proposed to explain the failure of these mediator-directed therapies, including the over-optimistic expectation that targeting a single inflammatory factor would be sufficient to modulate the complex host systemic inflammatory response. This has led to the rationale for non-specific elimination of circulating cytokines and other inflammatory mediators by continuous renal replacement therapies (CRRT) [6]. Ever since it was first proposed, the concept of cytokine removal with CRRT has been the subject of controversy. For example, it has been suggested that the high endogenous turnover of cytokines may limit meaningful extracorporeal clearance by routine methods of CRRT [7]. The current review aims to address whether and how cytokines and other inflammatory mediators can be removed efficiently by CRRT. Extracorporeal removal mechanisms and physicochemical characteristics of membranes affecting the elimination of inflammatory mediators are described, as are in vitro and in vivo studies on mediator induction and removal. The potential value of modifying routine CRRT techniques, e.g. high volume haemofiltration and the use of adsorptive devices, which aim to increase the efficiency of mediator removal, are also discussed. Finally, the concept of non-specific mediator removal is analysed in the light of the complex biological function of cytokines and the intricate interactions between pro- and anti-inflammatory networks.

The influence of CRRT on haemodynamic status, respiratory function and outcome in animal models and clinical studies has been reviewed elsewhere and lies beyond the scope of the present paper [8, 9].

Extracorporeal removal mechanisms and physicochemical characteristics of membranes

Several variants of CRRT have been developed, differing in terms of driving forces and clearance mechanisms. Continuous arterio-venous haemofiltration (CAVH) and continuous veno-venous haemofiltration (CVVH)
use convection as the main clearance mechanism, whereas continuous arterio-venous haemodialysis (CAVHD) and continuous veno-venous haemodialysis (CVVHD) also use diffusion to remove solutes.

Haemodialysis is achieved by diffusive clearance along a concentration gradient from blood to dialysate through a semi-permeable membrane. Small molecules diffuse rapidly and are efficiently removed, whereas larger solutes that diffuse poorly are cleared slowly. Haemofiltration is based on convective mass transport: a transmembrane pressure drives both fluid and solutes through a membrane selected for its high hydraulic permeability. The currently available membranes that have sufficient hydraulic permeability for haemofiltration are mainly synthetic: polysulphone (PS), polyamide (PA), polyacrylonitrile (PAN), polymethylmethacrylate (PMMA) and a copolymer of acrylonitrile and sodium methylallylsulphonate (AN69). Cellulose triacetate, a cellulosic membrane, can also be used. The extent of convective clearance is governed by the cut-off value of the membrane, as well as by the molecular weight, physicochemical characteristics and structure of the solute [10]. Molecules in the middle-to-large molecular weight range, such as many inflammatory mediators, are more efficiently cleared by convection than by diffusion.

In addition to diffusion and convection, adsorption has been found to be an important clearance mechanism with some dialysis membranes [11]. Protein adsorption onto polymers is mainly determined by hydrophobic interactions, by electrostatic interactions between zones with different polarities (Van der Waals), and by ionic bindings between dissociated chemical groups with opposite charges. Membranes with dense negative charges, such as the AN69 membrane, have a strong capacity to adsorb proteins. The accessibility of the polymeric chains also plays a major role in the adsorption process. In the case of the asymmetric microporous synthetic membranes (PS, PA, PAN, PMMA), adsorption is limited to the surface area of the pores. The AN69 membrane has the consistency of a hydrogel due to its dense and symmetrical structure and its high hydrophilicity. This characteristic favours contact of the blood compartment with all polymeric chains over the entire breadth of the membrane, thus making a larger surface area available for adsorption [12].

**In vitro studies**

Induction, adsorption and mass transfer of inflammatory mediators by biomaterials have been studied in various in vitro models.

Leukocytes produced modest quantities of IL-1 when cultured in the presence of PS, PAN or PMMA, but not in the presence of cuprophane (CU) [13]. When lipopolysaccharide (LPS) was added to the culture medium, the synthetic membranes induced the production of large amounts of IL-1 [13]. Interestingly, when incubated with monocytes, AN69 membrane fibres not only induced, but also bound, more IL-1 than CU [14]. In another study, AN69 fragments were incubated with radiolabelled IL-1/β and TNFα; substantial amounts of both cytokines bound to the AN69 membrane [15]. In an in vitro closed-loop dialysis circuit, the AN69 membrane cleared IL-1 by both dialysis and, primarily, adsorption; however, TNFα was less efficiently adsorbed and only minimally dialysed. In contrast, during CU haemodialysis the mass of both cytokines did not decline appreciably [14, 15]. Similarly, in an in vitro haemofiltration model, removal of TNFα was higher with AN69 than with PS and PA and was mainly due to adsorption. A subsequent partial release from the membrane was suggested by a negative blood clearance after 60–120 min [16]. The kinetics of TNFα and IL-1 were also studied in a single pass circuit with different dialysers (PS, PA, AN69 and cellulose acetate): there were modest convective losses of TNFα and IL-1 with the PS membrane, and of IL-1 with the AN69 membrane. In addition, there was substantial binding of TNFα and IL-1 to both AN69 and PA membranes. After 10 min, some of the previously bound TNFα was released from the PA membrane, suggesting that this was rapidly saturated [17].

Platelet activating factor (PAF) was effectively removed by convection through and by adsorption onto a PS membrane [18]. The AN69 membrane has a large adsorptive capacity for inactivated complement C3 and C5 [19], and for C3a [20]. Factor D, the rate-limiting enzyme of the alternative complement pathway, was efficiently adsorbed by AN69 [21] and PMMA [22], but not by cellulosic membranes. Some synthetic membranes may also adsorb endotoxins [23]; their permeability for endotoxins, however, remains a matter of debate [23, 24, 25].

In conclusion, several strands of evidence indicate that the synthetic membranes have a high adsorptive capacity for cytokines and complement components. In particular, the AN69 membrane appears to have a large capacity to adsorb, thus confirming the theoretical expectations based upon its physicochemical structure. In vitro convective removal of cytokines by synthetic membranes is modest, while diffusive clearance is minimal. It should be noted that any blood-membrane interaction also has the capacity to generate cytokines and activate complements, especially in the presence of LPS. However, the great propensity of synthetic membranes to subsequently adsorb these components compensates for this phenomenon. Saturation of the membrane and partial release of cytokines from their binding sites occurs after a certain time period.

Haemofiltration (CAVH or CVVH) with a synthetic membrane would appear to be the optimal strategy if