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REVIEW

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Can inflammatory cytokines be removed efficiently by continuous renal replacement therapies?

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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 methallylsulphonate (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-1β 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

elimination of inflammatory mediators is sought. The addition of a diffusive component (CAVHD or CVVHD) is probably not useful for inflammatory mediator removal. However, considerations based on theoretical principles and on in vitro findings may not reliably predict clinical findings.

Animal experiments

Data on mediator removal in animal models are scarce, probably because no reliable cytokine assays are available for animals. Heideman et al. demonstrated clearance of thromboxane-B_2 (TXB_2) and 6-keto-prostaglandin-$F_1\alpha$ (6-ketoPG$F_1\alpha$) by CAVH in rats with endotoxic shock. TXB_2 levels fell significantly in the CAVH-treated group [26]. Staubach et al. found a decrease of both mediators in endotoxaemic pigs that underwent CVVH [27]. CAVH has also been shown to have an immunomodulatory effect by attenuating polymorphonuclear phagocytosis during intra-abdominal sepsis in pigs [28].

Clinical studies

Studies examining the potential removal of inflammatory mediators by CRRT in critically ill patients are presented in Table 1 [29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55]. Most cytokines and complement components have a molecular weight below the cut-off value of the synthetic haemofiltration membranes. These mediators were detected in the ultrafiltrate of almost all haemofilters, although sieving coefficients were usually low. When simultaneous measurements of concentrations in pre-and post-filter plasma and in ultrafiltrate were performed, the quantities removed were substantially higher than could be explained by convective loss alone, suggesting other mechanisms of clearance [34, 53]. Our group has performed a detailed and quantitative analysis of the relative contribution of convection and adsorption to removal of selected cytokines with CVVH [55]. Adsorption appeared to be the most important clearance mechanism, especially immediately after the start of haemofiltration (Fig1). The longer the blood-membrane contact, the less clearance by adsorption occurred. Replacement of the haemofilter after 12 h of CVVH again increased adsorptive removal, indicating that saturation of the membrane was responsible for the rapid diminution of adsorption.

Even though most studies have shown evidence for convective and/or adsorptive removal of inflammatory mediators, few have demonstrated a significant decrease in plasma concentrations. We found a fall in plasma concentrations of all the cytokines measured 1 h after the start of CVVH and 1 h after the change of the membrane [55]. These effects were not sustained, however, corresponding with a rapidly diminishing removal rate. Millar et al. [39], Journois et al. [40] and Braun et al. [46] randomised patients to receive either haemofiltration or conservative treatment; a decrease of cytokine and complement levels was only demonstrated in the haemofiltration group.

Missing information and variability in study design make comparison of the in vivo performance of the different membrane types difficult. Only one study has analysed the effects of two membranes in the same patient group [49]. The plasma concentration of factor D fell with AN69 (mainly due to adsorption onto the membrane) but not when a PA membrane was used. Whether the proposed differences in adsorptive characteristics provide any clinical benefit remains open to discussion.

It has been suggested that high ultrafiltration rates are required to obtain significant mediator removal [6]. Blood flow rates (Q_B) and ultrafiltration rates (UFR) varied markedly between studies, but incomplete data again hinder any reliable comparison. The fall in plasma concentrations of C3a and C5a, but not of TNFα and IL-6, correlated linearly with the amount of withdrawn ultrafiltrate [40]. In another study [50], children undergoing cardiopulmonary bypass (CPB) were randomised to receive either standard haemofiltration to remove excess fluid or an additional period of zero-balance high volume haemofiltration during rewarming. C3a and TNFα levels fell during the high volume haemofiltration period and, interestingly, a delayed effect was observed on IL-1β, IL-6 and IL-8 levels. Furthermore, an improvement was observed in some clinical variables. The impact of the high volume per se cannot be properly assessed, as only one flow rate was studied. Our group has analysed the effect of a change in Q_B in the same patient population [55]. A Q_B of 200 ml/min was associated with a 75 % increase in ultrafiltration rate as compared to a Q_B of 100 ml/min. Cytokine removal increased significantly, due to more convective elimination but also to more membrane adsorption. To explain the latter phenomenon, we speculate that the higher transmembrane pressure drives solutes deeper into the membrane and thus increases the effective surface area available for adsorption. The observation that only minimal adsorption occurs when the ultrafiltrate line is clamped supports this hypothesis [56]. Kellum et al. compared mediator removal with CVVH and CVVHD in a crossover design and found decreased plasma TNFα levels only during treatment with CVVH [54]. They concluded that convection was the principal clearance mechanism, although only trace amounts of TNFα could be recovered from the ultrafiltrate. Their findings may, however, support the contention that a convective driving force is required for optimal adsorption.

Table 1 Clinical studies on mediator removal with CRRT

Author [Ref]	Study Population	Treatment	Membrane	Q_B[c] ml/m	Q_D[e] l/h	UFR[f] l/h	Mediator	Assay	UF[k]	PC[l]
Gotloib [29]	24 sepsis, ARDS	CAVH	CU	300			TXB_2	RIA[h]	+	
Coraim [30]	36 respiratory failure post cardiac surgery	CAVH	PS			0.85	Myocardial Depressant Factor	Bioassay	+	+
Staubach [31]	15 shock	CAVH	PA				6-ketoPGF$_1\alpha$ TXB_2	RIA	+ +	
McDonald [32]	12 sepsis, acute renal failure	CAVHD	AN69	116		0.6	TNFα TNFα IL-1*β*	Bioassay EIA[i] RIA	+ – +	– – –
Kierdorf [33]	10 MOF	CVVH	AN69			1.2	TNFα	EIA	+	–
Cotrell [34]	5 sepsis, acute renal failure	CVVHD	AN69				TNFα	Bioassay + IRMA[j]	+	
Byrick [35]	1 MOF, ARF	CAVHD	PS		2	0	TNFα	RIA	–	–
Tonnesen [36]	9 septic shock, acute renal failure	CAVH	PS			0.4–0.75	TNFα IL-1*β*, IL-6	EIA EIA	+ +	– –
Bellomo [37]	18 sepsis, acute renal failure	CVVHD	AN69	150	1		TNFα IL-1*β*	Bioassay EIA	+ +	– –
Andreasson [38]	9 cardiopulmonary bypass	HF[a]	PA				C3a C5a TCC[g]	RIA RIA EIA	+ +	– + –
Millar [39]	18 cardiopulmonary bypass	9 HF 9 no HF	PA				TNFα IL-6, IL-8	Bioassay EIA	+ +	+ –
Journois [40]	32 cardiopulmonary bypass	16 HF 16 no HF	PS				TNFα, IL-6 IL-8 C3a, C5a	EIA EIA RIA		+ – +
Gueugniaud [41]	4 burns, sepsis, acute renal failure	CVVHD					TNFα IL-1*β*, IL-2R IL-6	EIA EIA EIA	– + +	– – +
Elliott [42]	77	CAVHD/ CVVHD			0.9	0.56	TNFα IL-1*β*		+ +	
Bellomo [43]	10 sepsis, ARF	CVVHD	AN69	150	1		IL-6 IL-8	EIA EIA	+ +	– –
Sfyras [44]	20 sepsis, acute renal failure	CVVH					TNFα IL-6	EIA EIA	+ +	– –
Hoffmann [45]	16 MOF	CVVH	PA	150		2	TNFα, IL-6 IL-1*β*, IL-8, C5a, C3 C3a TCC	Bioassay EIA EIA EIA	– + + –	– – + –
Braun [46]	30 SIRS	15 CVVHD 15 conservative	PA/ AN69	100–120			TNFα, C3a IL-6, TCC	EIA EIA		– +
Boldt [47]	14 SIRS, acute renal failure	CVVH	PS	120–150			sELAM-1, sICAM-1 sVCAM-1, sGMP-140	EIA EIA EIA EIA		– – – –
Wakabayashi [48]	6 SIRS	CVVH					IL-6 IL-8			+ +
Gasche [49]	7 critically ill, acute renal failure	CVVH	AN69 PA	250 250		1–1.5 1–1.5	Factor D Factor D		–/+	+ –
Journois [50]	20 cardiopulmonary bypass	10 ZHVHF +HF[b] 10 HF	AN69	200[d]			TNFα, IL-1*β*, IL-6, IL-8 IL-10, C3a	EIA EIA EIA		+ + +
Heering [51]	33 acute renal failure (septic/ cardiovascular)	CVVH	PS	150–200		1	TNF-α, IL-1*β*, IL-6, IL-8 IL-2, IL-10 TNF-RII, IL-1ra IL-2R, IL-6R	EIA EIA EIA	+ + +	– – –

Table 1 Continued

Author [Ref]	Study Population	Treatment	Membrane	Q_B[c] ml/m	Q_D[e] l/h	UFR[f] l/h	Mediator	Assay	UF[k]	PC[l]
Sander [52]	26 SIRS	13 CVVH 13 conservative	AN69	150		1	TNFα IL-6		+ +	– –
van Bommel [53]	9 SIRS, acute renal failure	CAVHD	AN69		1		TNFα, sTNFR-I/II IL-1ra	EIA EIA EIA	+ + +	– – –
Kellum [54]	13 critically ill, acute renal failure	CVVH CVVHD	AN69	150–200		2	TNFα IL-6 IL-10, sL-selectin, ET	EIA EIA EIA	– + –	+[m] – –
De Vriese [55]	15 sepsis, acute renal failure	CVVH	AN69	100–200		1.5–2.7	TNFα, IL-1β,IL-6 IL-1ra sTNFR-I/II IL-10	EIA EIA EIA	+ + –	+ + +

[a] haemofiltration, [b] zero-balanced high-volume haemofiltration during rewarming in addition to standard haemofiltration, [c] blood flow rate, [d] per m^2 body surface, [e] dialysate flow rate, [f] ultrafiltration rate, [g] terminal complement complex, [h] radioimmunoassay, [i] enzyme-immunoassay, [j] immunoradiometric assay, [k] detectable in ultrafiltrate: + = yes, – = no, blank space = information not available, [l] effect on plasma concentration, [m] only for the CVVH group

Whereas it may be desirable to increase transmembrane pressure to a certain extent, the value of true high-volume haemofiltration, with ultrafiltration rates up to 6 l/h, remains to be determined. In animal models of sepsis, high-volume haemofiltration has been shown to improve haemodynamic and respiratory variables [8, 9], although no correlation was made with mediator removal. The application of this technique to the human situation raises substantial technical, organisational and financial obstacles. Although preliminary promising results have been presented [57], this approach still remains in the realm of experimental treatment.

Sorbent adsorption of endotoxin and cytokines

An alternative approach, which is only applicable to gram-negative sepsis, is extracorporeal removal of endotoxins with specific adsorption devices. Activated charcoal [58], polyethylenimine [59] and polymyxin B [59, 60] avidly bind endotoxin in vitro. Haemoperfusion using columns with immobilised polymyxin B efficiently removed endotoxins and decreased mortality in dogs after the injection of live *Escherichia coli* [60]. Preliminary clinical investigation in patients with endotoxic shock and multiple organ failure demonstrated that these devices may lower plasma endotoxin levels and improve haemodynamic status [61].

Plasma filtration coupled with sorbent adsorption is a recently developed technique whereby a plasmafilter is placed in series with a cartridge containing a sorbent consisting of charcoal and hydrophobic resin. The plasmafiltrate is circulated through the cartridge and re-infused back into the extracorporeal circuit. In vitro studies demonstrated substantial removal of both inflammatory and anti-inflammatory mediators [62]. A preliminary study reported a beneficial effect on haemodynamic status when compared to "classical" CVVH [63].

Several other adsorptive devices, primarily developed for use in chronic renal failure, are currently being investigated for their potential to adsorb inflammatory mediators [64].

The concept of non-specific removal of circulating cytokines questioned

Since solute removal with CRRT is non-specific, simultaneous elimination of inhibitors of inflammation may nullify any potential benefits of these therapies. Few studies have investigated the removal of anti-inflammatory mediators. Van Bommel et al. found an increase in the ratio of soluble TNF receptors to TNFα upon commencement of continuous haemofiltration [53]. In another study no change was seen in plasma levels of either pro- or anti-inflammatory cytokines [51]. We have found equivalent removal rates of inhibitors of inflammation and inflammatory cytokines [55]. In particular, we found no change in the ratios of soluble TNF receptors to TNFα, and of IL-1ra to IL-1β during CVVH. However, simple ratios between selected cytokines and their inhibitors probably do not predict the effect of a CRRT on the complex interaction between the pro- and anti-inflammatory system. More work is required to clarify this important issue.

Several studies have found correlations between circulating levels of inflammatory cytokines and outcome of patients with sepsis [2]. However, it remains unclear to what extent circulating cytokines contribute to the inflammatory reactions occurring locally in affected organs during sepsis/SIRS, or whether they are merely indirect markers of the severity of the disease process. As yet, the clinical benefit of their removal remains to be proven.

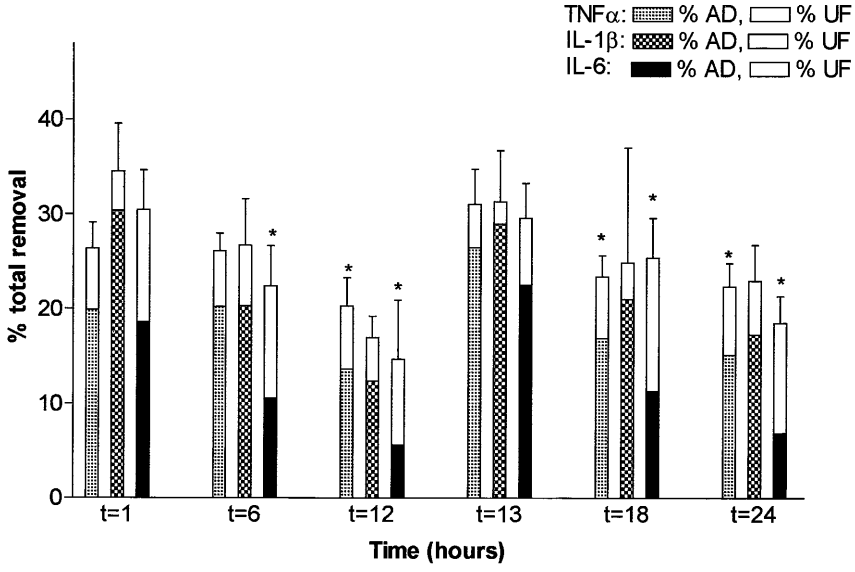

Fig. 1 The total amount of TNFα, IL-1β and IL-6 that was removed (expressed as a percentage of the amount present in the prefilter plasma) at different time points after the start of CVVH in 15 patients with septic shock and acute renal failure. After 12 h (t = 12) the haemofilter was replaced. The removed amount at t = 6 and 18 and at t = 12 and 24 was significantly lower than at t = 1 and t = 13 (*$p < 0.05$). The relative contribution of adsorption (% AD, *hatched bars*) and ultrafiltration (% UF, *open bars*) is indicated for each value. No statistical analysis was performed for IL-1β, since it was detected in only five patients ([55], with permission)

An important lesson may be learned from the experience with haemofiltration during cardiopulmonary bypass (CPB), which is known to induce a systemic inflammatory response. As discussed previously, a course of zero-balanced haemofiltration during rewarming from CPB was shown to have delayed beneficial effects: cytokine levels were lower 24 h after surgery, suggesting the earlier removal of mediators triggering their release [50]. Importantly, an improvement was noted in several clinical variables. It thus appears that, when applied at a very early stage, haemofiltration may have the potential to down-regulate a systemic inflammatory response, possibly by removing early mediators. However, the trigger to SIRS is usually not predictable and most critically ill patients have evolved far beyond this early phase when they are considered for haemofiltration.

Conclusion

Various studies have demonstrated that inflammatory mediators can be removed during CRRT, by convection, but mainly by membrane adsorption. In most studies, removal was not important enough to result in a significant and sustained effect on plasma concentrations. An analysis of in vitro and in vivo data suggests that this low efficiency may result from rapid saturation of the easily accessible binding sites on the membrane, and to inefficient use of less accessible binding sites due to a low convective driving force. Optimal mediator removal may thus be obtained by a combination of a high transmembrane pressure and frequent membrane changes. Frequently changing the membrane does appear to be both expensive and impractical, therefore the use of adsorptive devices could be a valuable alternative. However, these devices are still at a developmental stage. The recently developed technique of continuous plasmafiltration coupled with sorbent adsorption has shown promising preliminary results.

Since the financial implications of these measures are important, it is crucial to see whether it makes sense to remove inflammatory mediators non-specifically from the circulation of patients with established SIRS. The pathogenetic role of circulating cytokines should be clarified. Furthermore, it should be established whether concomitant removal of anti-inflammatory mediators does not counteract any potential beneficial effects.

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