Commentary

Hemofiltration, adsorption, sieving and the challenge of sepsis therapy design

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Abstract

Circulating inflammatory mediators spilling into the circulation from sites of active inflammation are considered the source of remote tissue injury and associated organ dysfunction in sepsis. Hemofiltration has been proposed as a therapy for sepsis based on its ability to remove circulating inflammatory mediators by sieving or by adsorption, or both. Designing devices and methods for sepsis therapy will require optimization of these two mechanisms. In the present issue of *Critical Care Forum*, Kellum and Dishart report the relative effects of sieving and adsorption on plasma IL-6 following cecal ligation and puncture in rats. The authors conclude that hemoadsorption is the main mechanism of removal, and discuss some possible implications for filter design but hemoadsorption is well dependant on hemofiltration (the so-called hemofiltration filter adsorption/synergistic effect). It is important to recognize the limitations of conventional systems; Kellum and Dishart have extended our knowledge of hemofiltration filter adsorption, which is quite different from conventional hemoadsorption. If sepsis is a manifestation of a nonlinear dynamic control system out of control, then filtration at modest doses with a large pore filter may succeed as well as high-volume hemofiltration with a conventional cut-off filter. In the present paper, we will explore the strengths and the weaknesses of the 'Kellum and Dishart' study and discussing their findings in the light of the current available literature.

Keywords adsorption, hemofiltration, membrane, sepsis, sieving

Circulating inflammatory mediators (IM) spilling into the circulation from sites of active inflammation are considered the source of remote tissue injury and associated organ dysfunction in sepsis. Hemofiltration has been proposed as a therapy for sepsis based on its ability to remove circulating IM by sieving or by adsorption, or both. Designing devices and methods for sepsis therapy will require optimization of these two mechanisms. In the present issue of *Critical Care Forum*, Kellum and Dishart report the relative effects of sieving and adsorption on plasma IL-6 following cecal ligation and puncture in rats [1]. The authors conclude that hemoadsorption is the main mechanism of removal, and discuss some possible implications for filter design. Hemoadsorption is dependent on membrane material and filtration operating parameters (e.g. filtration fraction: the so-called adsorption/synergistic effect).

If hemofiltration is to be an effective therapy in the complexity of sepsis, then proper design of its material and operational characteristics must be pursued. Adsorption of proteins to membrane materials is well recognized in pharmaceutical manufacturing, food processing and medical filtration. The type and extent of feed solution proteins adsorbed depends on the membrane material, the pH, ionic strength and composition of the feed solution, the pore size, the membrane morphology and the presence of a polarization layer.

Membrane materials vary in the extent and type of cytokines adsorbed. Data from *in vitro* studies reveal tumor necrosis factor adsorption of 30–32% for polyamide and AN69, and of 0% for cellulose acetate and polysulfone. IL-1 adsorption

IL = interleukin; IM = inflammatory mediators; MWCO = molecular weight cut-off; SC = sieving coefficient.

was 40% for polyacrylonitrile, 0–11% for polysulfone, 2% for AN69 and 0% for polyamide [2,3]. Birk *et al*. found an approximately sixfold difference in total plasma protein adsorption between different membrane materials. Total protein adsorption was negatively correlated with the adsorption of proteins with molecular weight < 65 kDa [4].

The feed solution pH and ionic strength significantly affect adsorption and polarization, as shown *in vitro*. At pH 4.8, the sieving coefficient (SC) for albumin and the SC for IgG are ~0.45 and 0, respectively. At pH 7.4, however, these SCs are 0.38 and 0.85, a substantial reversal [5]. At equal concentration, mixtures of IgG and albumin reduce filtrate flux and protein diffusivity more than pure solutions; this results from protein–protein interactions [6]. Generally, these factors cannot be manipulated in clinical hemofiltration.

Membranes with a higher molecular weight cut-off (MWCO) adsorb more protein than lower MWCO membranes. Uptake of radiolabeled albumin by a 100 kDa MWCO polysulfone membrane was nearly double that of a 30 kDa MWCO membrane [7]. Protein uptake occurred preferentially in larger pores [8]. This pattern of protein uptake has significant implications for molecular sieving. Molecular sieving in AN69 membranes was characterized using polydisperse dextran before and after blood contact. The SC for dextran of molecular weight < 5 kDa was reduced by 14%, and the SC for 20 kDa dextran was reduced by 60% [9].

Protein (including cytokine) adsorption and polarization of filtration membranes have been extensively studied. Awareness of these characteristics is essential in designing filtration therapy for sepsis. Some design elements relevant to adsorption are fixed for a given system (e.g. membrane materials, morphology and surface area), and some do not permit manipulation (e.g. patient plasma protein composition, pH and ionic strength). However, as membrane adsorption is rapidly saturated (30 to 50 minutes) [9,10]. Recent recognition that the intensity of ultrafiltration needs to be adjusted for patient body size and severity of illness [11,12] supports the need to focus on sieving and filtrate flow as promising points for new designs.

The design of blood filtration in sepsis should focus on those characteristics of hemofiltration that permit greater effectiveness in controlling sepsis and that provide operational flexibility so the therapy may be tuned to patient body size and severity of illness. This process begins with recognition of key features of the inflammatory response. The network of IM, acting as a nonlinear dynamic control system, drives the inflammatory response [13,14]. Network effects make the inflammatory response robust against large narrowly focused changes [15]; this robustness probably explains the failure of drugs directed against some single IM [14]. Control networks may be manipulated by application of small changes in the activity to many network elements. The more elements (e.g. IM) affected, the smaller the change in their aggregate activity required for system control. Applied to blood filtration in sepsis, either high doses of filtration with a conventional filter, or lower doses with a large pore filter should be effective.

In their study, Kellum and Dishart used an appropriate animal model (ceacal ligation and puncture) relevant in its initial insult and delay in treatment. According to the average body weight for adult, male Sprague-Dawley rats reported (486 g) and to the ultrafiltration flow rate(Quf) reported (30 ml/hour), we can conclude that a dose of ~62 ml/kg (which for a 75 kg human being represent 4.5 l/kg per hour) was delivered.This dose is greater than the highest dose used by Ronco *et al.* (45 ml/kg per hour) [11] and clinically relevant as high-volume hemofiltration is usually defined to be greater than 50 ml/kg per hour [16]. However when looking at literature, usual average body weight for adult, male Sprague-Dawley rats is about 580 g [17].

In the study of Kellum and Dishart, Quf was not controlled or indexed to body weight. Recent [11,12] demonstrations of dose-response effects of hemofiltration in human acute renal failure and sepsis make indexing Quf to body weight a critical parameter to assess or control. Filter blood flow was spontaneous and not quantified; however the high Quf suggest an high filtration fraction prevailed. Low filtration fraction promotes IM sieving, high filtration fraction promotes adsorption and reduces sieving of IM [18].

What evidences support effective sieving of IM in sepsis? Honore *et al*. replaced 35 l of ultrafiltrate in 4 hours (using high-volume hemofiltration) in 20 patients with refractory septic shock using a polysulfone membrane (Fresenius, MWCO = 35 kDa) [12]. Predicted mortality for the group was 79%, and observed mortality was 55% ($P < 0.05$). Patients who responded (improved to specified end points) hemodynamically by the end of the 4 hours survived significantly more often (9/11) than those patients that did not respond (0/9 survived 24 hours).

Retrospective analysis of the study of Honore *et al*. [12] revealed that responders were smaller (66.2 ± 8.4 kg) than nonresponders (82.6 ± 13.4 kg) and therefore received a larger dose of filtration (0.53 ± 0.07 l/kg per 4 hours [±150 ml/kg per hour of hemofiltration clearance indexed to body weight and time] and 0.43 ± 0.07 l/kg per 4 hours [±110 ml/kg per hour of hemofiltration clearance indexed to body weight and time], respectively). Retrospective analysis of the study of Honore *et al*. [12] suggests that a sufficiently high dose allows ~82% improvement in survival. The same protocol applied to all patients, thus adsorption should be similar in all patients; adsorption should be saturated by 30 to 50 minutes [9,10]. Thus the dominant mechanism of IM removal should be sieving. Survival was not assess in the study of Kellum and Dishart [1].

Table 1

Sieving coefficients of large pore membranes and conventional pore membranes

		Cytokine					
Membrane	Operating characteristics	IL-8 (MW = 8 kDa)	TNFα (MW = 17 kDa)	IL-1 (MW = 17 kDa)	IL-10 (MW = 17 kDa)	IL-6 (MW = 26 kDa)	Albumin (MW = 69 kDa)
100 kDa polyamide [20]	1 l/h	0.31	0.27	0.81	0. 56	0.73	0.06
	6 l/h	0.19	0.09	0.75	0. 56	0.32	0.0
Polyamide* [21]	Variable	0.25	0	0.18		0	
Polysulfone* [22]		0.12	0.22	0.42	0	0.04	
AN69** [23]		0.08	0.16	0.22	0	0.18	

TNFα, tumor necrosis factor alpha; MW, molecular weight. Mean molecular weight cut-off (MWCO) of 30 kDa is shown in the table by the sign * and the MWCO of 50 kDa is shown in the table by the sign **.

A large pore filter (polysulfone, MWCO = 100 kDa) has been used in a swine model of lethal sepsis [19]. In a paired study with a similar conventional filter (MWCO = 50 kDa), and using identical operating parameters (e.g. equal filtration fraction) the 100 kDa filter was associated with a survival time nearly twice that of the 50 kDa filter. A similar filter (polyamide, MWCO = 100 kDa) has been studied *in vitro* by Uchino *et al*. using recirculating human blood [20]. The blood was spiked with endotoxin to raise a cytokine response. Selected results are compared in Table 1 with conventional filters [20–23].

The 100 kDa membrane has two significant advantages. First, for IM sieved by conventional and the 100 kDa membrane, the 100 kDa exhibits higher SC. Second, the 100 kDa sieves cytokine not sieved by conventional membrane.

If sepsis is a manifestation of a nonlinear dynamic control system operating at an excessive and injurious level, then filtration at modest doses with a large pore filter may succeed; high-volume hemofiltration with a conventional MWCO should also be effective.

A successful blood filtration therapy for sepsis and septic shock will not be found by accident – it will be designed. It is important to recognize the limitations of conventional systems. Kellum and Dishart have shown that hemofiltration filter adsorption occurs and exhibits meaningful biologic effects.

The design of successful blood filtration therapy in sepsis will require recognition of the limitations of existing systems and methods. The Kellum and Dishart study aids this recognition. Recognition that IM are not operative as single agents, but are closely integrated in a self-regulated control network [13–15] is of key importance to design of therapeutic systems. A blood filtration system which filters a sufficiently wide of IM to be effective in sepsis, and has the operation flexibility to readily adapt to patients of different body size and severity of illness will require careful design. In matters of membrane separation and system control, our engineering colleagues have much to offer.

Partnering with industry and engineering should allow new devices and methods to be developed and tested. This should be done before we embark upon a large scale multicentre study [24]. By viewing the whole problem, we can work out the whole solution.

Competing interests

None declared.

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