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HEMOFILTRATION IN HUMAN SEPSIS: EVIDENCE FOR ELIMINATION OF IMMUNOMODULATORY SUBSTANCES

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CONTINUOUS HEMOFILTRATION (HF) is widely used for renal replacement therapy in patients who develop kidney failure as part of a multiple organ dysfunction syndrome (MODS). In these patients we demonstrated a correlation between the daily amount of ultrafiltrate and the survival rate.[1] It has been suggested that HF may eliminate toxic mediators of MODS.[2] The present study examined whether HF can activate or eliminate established mediators in patients with septic MODS. Because the exact nature of the factors removed remains unclear, it appeared feasible to evaluate the biological effect of ultrafiltrate by exposing it to several white blood cell subfractions in vitro.

MATERIALS AND METHODS

Continuous isovolemic veno-venous HF was performed using a fiber hemofilter (FH 66, Gambro, Hechingen, FRG) and a flow-controlled roller pump (filtration rate: 2 L/min) in 16 patients with septic MODS (Elebute and Stoner[3] scorepoints ≥20) and in five healthy volunteers. Pre- and postfilter and ultrafiltrate concentrations of cytokines (interleukin [IL]-1β, IL-6, IL-8, tumor necrosis factor [TNF]-α) and of complement compounds (C3, C3a, C5a, C5b-9) were measured shortly after the beginning of HF (t_0) and 60 minutes later (t_{60}). Healthy peripheral blood mononuclear cells (PBMC) and lymphocytes were incubated with ultrafiltrate and stimulated with endotoxin and phytohemagglutinin (PHA), respectively. Cell function was determined by measuring concentrations of several released cytokines in the supernatants and by PHA (0.5 μg/mL)-induced ^{3}H-thymidine uptake. Isotonic saline solution (NaCl) served as control. All data are expressed as

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Table 1—TNF, IL-6, and IL-1 release of human peripheral blood mononuclear cells (PBMC) and IL-2 and IL-6 release of lymphocytes in vitro

	Septic patients (n = 16)			Healthy volunteers (n = 5)		
PBMC	Ultrafiltrate at t_0	Ultrafiltrate at t_{60}	NaCl controls	Ultrafiltrate at t_0	Ultrafiltrate at t_{60}	NaCl controls
TNF (U/mL)	41.0 ± 10.0†	40.2 ± 10.7†	12.8 ± 4.3	26.5 ± 8.6	31.2 ± 12.1	23.8 ± 7.8
IL-6 (U/mL)	2,015 ± 466	1,485 ± 244	2,006 ± 255	1,518 ± 212	1,471 ± 294	1,398 ± 175
IL-1 (pg/mL)	966 ± 256	n.d.	946 ± 183	935 ± 211	n.d.	936 ± 173
Lymphocytes						
IL-2 (U/mL)	0.35 ± 0.07†	n.d.	0.66 ± 0.07	0.48 ± 0.18	n.d.	0.41 ± 0.12
IL-6 (U/mL)	4,295 ± 896*	3,093 ± 741†	6,496 ± 873	5,879 ± 2,670	5,316 ± 1,833	5,433 ± 1,497

Cultures were costimulated with endotoxin (1 μg/mL) and phytohemagglutinin (2.5 μg/mL), respectively. Cells were incubated with septic or healthy ultrafiltrate collected at t_0 and t_{60}. Ultrafiltrate and corresponding NaCl incubations were always performed in the same cell preparation.
*$P < 0.01$ vs. NaCl; †$P < 0.001$ vs. NaCl; n.d. = not determined.

mean ± SEM. The differences between the incubation procedures and between means of different time points were compared with the Student's *t*-test. A significance level of $P = 0.01$ was used throughout the study.

RESULTS

HF showed no signs of mediator activation, since the most sensitive parameter (pre/postfilter C5b-9 concentration difference) remained unchanged during treatment. Prefilter concentrations of cytokines were constant during HF, although IL-1 and IL-8 were detected in the ultrafiltrate. Prefilter C3a concentration significantly declined during HF (patients: $t_1 = 676.9 \pm 99.7$ ng/mL, $t_2 = 545.4 \pm 83.2$, $P < 0.001$; volunteers: $t_1 = 54.82 \pm 13.25$ ng/mL, $t_2 = 33.9 \pm 10.68$, $P < 0.001$) and C3a appeared in ultrafiltrates. Septic ultrafiltrate enhanced endotoxin-induced TNF-α release in PBMC and suppressed PHA-induced lymphocyte IL-2 and IL-6 production (Table 1). PBMC proliferation was suppressed by septic ultrafiltrate compared to NaCl (septic ultrafiltrate at t_0: 14,754 ± 1,534 cpm vs. NaCl: 37,418 ± 160 cpm; $P < 0.001$). Ultrafiltrate from volunteers did not cause significant changes.

CONCLUSIONS

Blood–membrane contact during hemofiltration does not appear to activate mediators of MODS. Certain factors such as C3a, but not established cytokines, are effectively eliminated by HF. Ultrafiltrate from patients with MODS contains a mixture of mediators, which induces changes in healthy white blood cell function with similarity to the septic response. HF represents a new modality of mediator removal in situations calling for an attenuation of an exaggerated monocyte TNF production and a stimulation of suppressed lymphocyte function.

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