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Cytokine Patterns in Patients Who Undergo Hemofiltration for Treatment of Multiple Organ Failure

Thomas Koperna, M.D., Sonja E. Vogl, M.D., Gerald P. Pöschl, M.D., Gerhard Hamilton, P.D., G. Röder, M.D., Peter Germann, M.D.

Department of Anesthesiology and General Intensive Care, University of Vienna, Währinger Guertel 18-20, A-1090 Vienna, Austria

Abstract. The excessive uncontrolled activation of inflammatory cells and mediators after trauma or major surgery plays a key role in the development of adult respiratory distress syndrome and multiple organ system failure (MOSF). In the past elevated cytokine levels were shown to influence the outcome of these patients adversely. There are diverging results regarding the removal of circulating cytokines by various methods of hemopurification for clinical improvement of MOSF. Seven patients after trauma or major surgery underwent continuous venovenous hemofiltration (CVVH) for the treatment of severe organ failure of the heart and lungs (Murray score 2.74) but not for renal or liver failure. The cytokine levels were measured at the beginning and 15, 60, 120, and 240 minutes after initiation of CVVH (measure points MP1–5). Clinical improvement during the treatment was monitored, and correlation with cytokine levels was evaluated. Arterially measured tumor necrosis factor α rose from 11.14 ng/ml to 17.86 ng/ml ($p < 0.05$). Arterial interleukin-6 (IL-6) levels significantly decreased during CVVH from 1284.7 ng/ml to 557.9 ng/ml; IL-8 levels simultaneously decreased from an initial peak of up to 154.4 ng/ml at MP3 to 97.3 ng/ml at MP5. The drop in serum IL-6 and IL-8 levels closely correlated with clinical improvement. After 2 hours of CVVH the hemodynamic situation improved significantly, as revealed by a decrease in catecholamine expenditure, an increase in arterial pressure, and a decrease in pulmonary artery pressure. Moreover, 2 hours after the initiation of CVVH the oxygenation index rose significantly and correlated well with the drop in shunt fraction. The Murray score significantly fell to 1.86. The removal of IL-6 and IL-8 by CVVH after initial stimulation correlates with clinical improvement, which was demonstrated by significantly improved oxygenation and hemodynamics from 2 hours after the initiation of CVVH onward. The elimination of cytokines and several mediators by CVVH may contribute to the cardiopulmonary improvement of critically ill patients. In comparison with the clinical control group ($n = 7$), which was comparable in terms of MOSF, no intervention led to a similar improvement in cardiorespiratory failure, and overall two of these patients died. Moreover, patients of the control group experienced a significant longer stay at in the intensive care unit.

Hemopurification is well known for its advantages in critically ill patients with renal failure. Recently, hemofiltration emerged as a tool to eliminate putative circulating mediators initiating systemic inflammatory response syndrome (SIRS) by trauma, shock, or infection [1–3]. The proinflammatory cytokines tumor necrosis factor-α (TNF-α), interleukins 6 and 8 (IL-6, IL-8) are known to play pivotal roles in SIRS, and they trigger hemodynamic and respiratory dysfunction [4–6]. Although blood purification procedures may induce some cytokine release [7], the beneficial effects of blood purification come to the fore [4, 7, 8]. Investigations on the effects of hemopurification on cytokines are complicated by the fact that cytokines possess synergistic as well as opposing effects and have common proinflammatory properties.

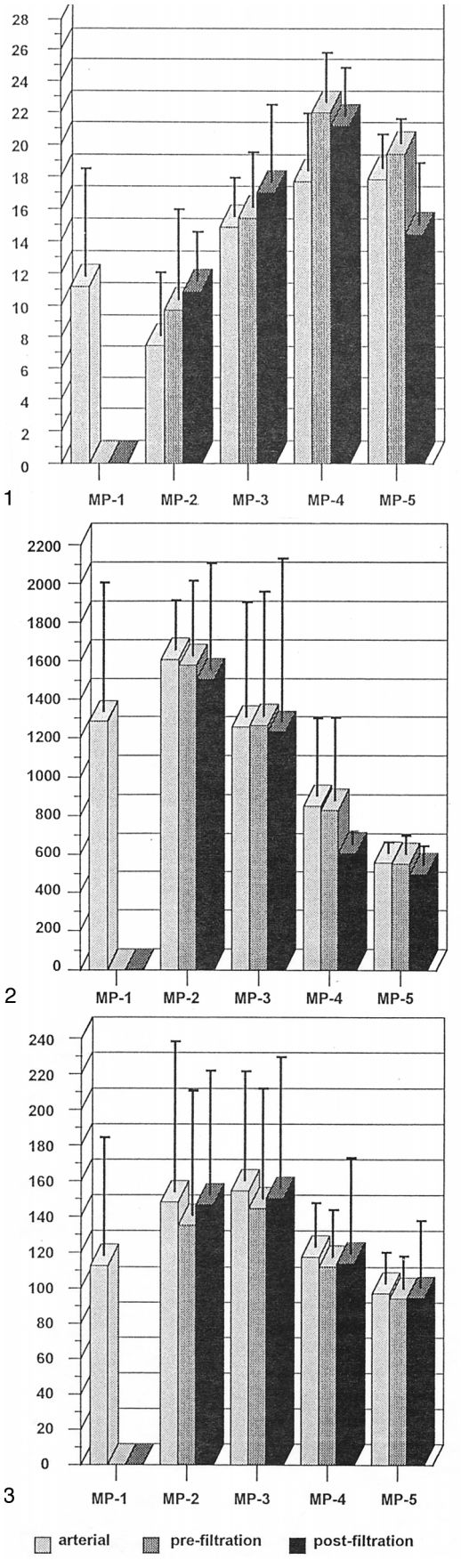
Continuous methods of blood purification have been applied in patients with multiple organ system failure (MOSF) [9, 10], with the expectation that it could help to treat or prevent MOSF by acting as an artificial kidney or liver and removing humoral mediators [1, 11, 12]. The aim of our study was to investigate patients with no renal or hepatic failure but with SIRS, established adult respiratory distress syndrome (ARDS), and hemodynamic failure after trauma or major surgery. All the patients underwent continuous venovenous hemofiltration (CVVH) for treatment of MOSF. Cytokine serum levels corresponding with the improvement of hemodynamic and respiratory function were measured routinely to unravel the pathophysiology of MOSF. A control group comparable in respect to MOSF is presented to demonstrate the clinical improvement in the study group.

Patients and Methods

We investigated seven individual CVVHs in patients of both sexes (four women, three men) with a mean age of 43 ± 13.2 years (range 23–62 years). The initial APACHE II score averaged 16.5 ± 7.2 (range 10–26). The patients had undergone either trauma or major abdominal surgery. Patients with a neoplastic disease were excluded. In each case an arterial line, a pulmonary artery catheter, and a central venous dialysis catheter were placed. All patients were sedated with midazolam and sufentanil and were mechanically ventilated. CVVH was deemed necessary in the presence of cardiopulmonary failure [9, 10] requiring catecholamine doses exceeding, for norepinephrine, 0.1 μg/kg/min or for dobutamine 10 μg/kg/min, ventilator settings of more than 0.4 inspired oxygen fraction (FiO_2), and a positive end-expiratory pressure (PEEP) $\geq$ 10 cm H_2O. Patients with renal or hepatic failure were excluded from the study.

To compare these patients with cardiopulmonary failure but no failure of the liver and kidneys, another seven patients (four men, three women) comparable in terms of MOSF, age, and cause of

Correspondence to: P. Germann, M.D.



admission to the intensive care unit (ICU) were examined. The patients of the control group underwent comparable conservative treatment but no CVVH. The mean age was 43.9 ± 10.5 years (range 27–60 years), and the initial APACHE II score averaged 15.3 ± 6.6 (range 7–25).

Blood samples were withdrawn from an arterial line before (pre-HF) and after (post-HF) hemofiltration (Diafilter-30 hemofilter; Amicon Division, Grace & Co., Beverly, MA, USA). The first sample was withdrawn 15 minutes prior to CVVH (measure point 1, MP1) and immediately processed as described later. The following samples were drawn from arterial pre-HF and post-HF sites simultaneously at measure points 15 minutes (MP2), 60 minutes (MP3), 120 minutes (MP4), and 240 minutes (MP5) after the initiation of CVVH. The serum was centrifuged at 2500 rpm and 4°C and then divided into three aliquots and stored at −80°C until further processing.

The CVVH was performed using Equaline BP 11; priming was done with isotonic saline solution and heparin following standard operating procedures; and the filtration fluid was substituted with hemofiltration solution (HAEMFL-MD solution; Leopold, Graz, Austria). The solution's contents per 1000 ml were Na^+ 142 mmol, Ca^{2+} 2.0 mmol, Mg^{2+} 0.75 mmol, Cl^- 103 mmol, L-lactate 44.5 mmol, glucose 1.5 g. Hemofiltration was maintained at a rate of 200 ml/min; the quantity of the ultrafiltrate was 60000 ml ± 1500 ml/24 hr. Cytokine levels were evaluated with electroimmuno assay (EIA) (Biomedica Quantikine IL-8, Biomedica Immunotech EIA-IL-6, EIA-TNF-α).

Hemodynamic and oxygenation data were evaluated by means of the heart rate, mean arterial pressure, cardiac index, pulmonary capillary wedge pressure, mean pulmonary arterial pressure, pulmonary right–left shunt fraction, and the oxygenation index (PaO_2/FiO_2). Respirator settings remained unchanged except for the FiO_2, whereas the catecholamine dosage was adapted to pathophysiologic findings during the investigation period.

Additionally the ARDS score according to Murray was assessed in every patient [13]. Using this scoring system the following data were evaluated on a 4-point scale and the mean value calculated thereafter: PaO_2/FiO_2 ratio, PEEP, compliance, and a radiograph of the chest.

Statistics were calculated using the Wilcoxon rank-sum test, and correlation was computed by the Spearman median correlation coefficient. The level of significance was set at $p < 0.05$.

Results

The TNF-α measured at the arterial line initially declined from 11.1 ng/ml to 7.4 ng/ml at MP2 and subsequently rose to 17.9 ng/ml at MP5 ($p < 0.05$) (Fig. 1). The pre-HF and post-HF values

Fig. 1. TNF-α levels measured arterially before and after hemofiltration prior to CVVH and 15, 60, 120, and 240 minutes after application of CVVH (MP1–5).

Fig. 2. IL-6 levels measured arterially before and after hemofiltration prior to CVVH and 15, 60, 120, and 240 minutes after application of CVVH (MP1–5).

Fig. 3. IL-8 levels measured arterially before and after hemofiltration prior to CVVH and 15, 60, 120, and 240 minutes after application of CVVH (MP1–5).

Table 1. Clinical improvement during CVVH measured by catecholamine expenditure and respiratory and hemodynamic parameters.

Parameter	MP1	MP2	MP3	MP4	MP5
I/E ratio	1:1	1:1	1:1.5	1:1.5	1:1.5
PaO_2/FIO_2	116.2 ± 12.3	130.7 ± 15.5	167.9 ± 21.2	191.7 ± 21.2*	212.9 ± 21.3*
Qs/Qt (%)	3.30 ± 2.8	30.0 ± 3.1	25.0 ± 2.2	19.0 ± 1.8*	18.0 ± 1.2*
Norepinephrine (μg/kg/min)	0.12 ± 0.04	0.10 ± 0.02	0.08 ± 0.02	0.050 ± 0.012*	0.022 ± 0.01*
Dobutamine (μg/kg/min)	12.0 ± 2.3	10.0 ± 2.0	8.3 ± 1.2	6.4 ± 0.8*	5.3 ± 0.5*
Heart rate (bpm)	115 ± 12	113 ± 15	93 ± 5	87 ± 4*	82 ± 5*
MAP (mmHg)	62 ± 7	69 ± 6	75 ± 7	81 ± 3*	87 ± 4*
CI (L/m^2)	5.9 ± 1.2	5.6 ± 1.3	4.9 ± 0.9	4.7 ± 0.7	4.6 ± 0.6
PCWP (mmHg)	16.0 ± 3.7	15.0 ± 3.2	12.0 ± 2.2	10.0 ± 2.4*	7.0 ± 1.2*
MPAP (mmHg)	28.0 ± 2.9	26.0 ± 1.9	20.0 ± 2.2	17.0 ± 1.7*	16.0 ± 1.5*
Fluid balance (ml)	0	−50	−200	−400	−800

I/E: inspiratory/expiratory; PCWP: pulmonary capillary wedge pressure; MPAP: mean pulmonary arterial pressure; Qs/Qt: pulmonary shunt fraction; PCWP: pulmonary capillary wedge pressure. See text for explanations of other abbreviations.

*Data with significant improvement during therapy ($p < 0.05$).

showed the same tendency at MP1 to MP4, but the TNF-α values first dropped at MP5, whereas the arterial TNF-α showed stagnation. IL-6 measured at the arterial line showed an initial increase and then continuously fell to 557.9 ng/ml thereafter (Fig. 2). An identical tendency was observed in the IL-6 values in both the pre-HF and post-HF samples.

Arterial IL-8, which is known to be stimulated by TNF-α, peaked at 154.5 ng/ml at MP3 and subsequently decreased to 97.3 ng/ml at MP5 (Fig. 3). With regard to venous IL-8 the pre-HF and post-HF values were also close to the arterial IL-8 values.

Because of extracorporeal circulation the patients' core temperature fell from 37.6 ± 0.3°C to 35.7 ± 0.2°C at MP3. This temperature was kept stable throughout the observation period.

Arterial IL-6 and IL-8 showed a transient increase after the initiation of CVVH, followed by a significant decrease starting 60 to 120 minutes later. For IL-6 and IL-8, a significant correlation could be observed at all sample sites, presenting a constant decline of cytokine levels during CVVH. The arterial TNF-α increased significantly during the observation period, though stagnation was found at MP5, whereas in the post-HF line a decrease was already apparent at MP5. At this time the decrease in the post-HF line was visible as a tendency but was not significant.

Clinical improvement during CVVH was impressive in our patients (Table 1). The need for catecholamines (both norepinephrine and dobutamine) was significantly reduced by hemofiltration after 120 minutes. Regardless of the reduction in catecholamine expenditure, the heart rate fell from 115 ± 12 bpm to 82 ± 5 bpm, and the mean arterial pressure (MAP) increased from 62 ± 7 mmHg to 87 ± 4 mmHg. Overall, cardiovascular function was markedly improved after only 4 hours of CVVH. The initially high pulmonary pressures could be reduced to an average level by means of a mean negative fluid balance of 800 ml. Hyperdynamic cardiovascular failure was a sign of the systemic inflammatory state and was demonstrated by a cardiac index (CI) of 5.9 ± 1.2 C/m^2 in our patients. The cardiac index was markedly improved during CVVH.

Respiratory function continuously improved during CVVH. The oxygenation index (PaO_2/FIO_2) and the pulmonary shunt fraction (Qs/Qt) after 2 hours of CVVH revealed a significant improvement in respiratory function. The mean initial Murray score was 2.74 and improved to 1.86 after treatment ($p < 0.05$). In the control group the initial Murray score averaged 2.67 and was not improved by diuretics, mechanical ventilation with body position changes, permissive hypercapnia, or other means of conservative treatment within 4 hours of therapy.

Notwithstanding the severity of illness, all patients of the treatment group survived. Similar clinical improvement could not be achieved in the control group over the same period of time. Overall, two patients of the control group died because of cardiopulmonary failure. However, this difference in clinical mortality showed no significance. The duration of stay in the ICU averaged 27.4 ± 9.2 days in surviving patients, whereas patients who underwent CVVH required a mean ICU stay of 16.3 ± 4.9 days, which represents a significant difference ($p < 0.05$).

Discussion

The cascade of mediators present were triggered and consecutively disturbed by traumatic or inflammatory assault. Cytokines rise to high levels shortly after the onset of activation [14–17]. Endothelial damage in cases of sepsis, ARDS, and MOSF probably results from persistent and repetitive inflammatory insults [16].

It has been pointed out that blood purification can also release cytokines by activating complement via passage of microbial products from the dialysate or leukocyte activation when passing through the fibers of the hemofilter [7, 18, 19]. Furthermore, the high molecular weight of TNF-α and protein binding may contribute to the poor results of blood purification [19–21]. Indeed, we demonstrated an increase in serum TNF-α levels during the observation period. Others have demonstrated significant removal of cytokines by blood purification [11, 12, 22]. In contrast, Hoffmann et al. proposed that hemofiltration effectively eliminates immunomodulatory mediators but not cytokines [23]. After an initial increase in IL-6 and IL-8, we observed a significant reduction in serum IL-6 and IL-8 levels during CVVH in our patients. A physiologic reduction of circulating cytokines to average levels is possible only in patients with normal hepatic and renal function. In patients who suffer from hypercatabolic SIRS, the physiologic capacity of the liver and kidneys to react efficaciously may be overcharged. Cytokine elimination [22] may show

a significant clearance much above the plasma clearance but fails to lower the plasma cytokine concentration. Therefore although plasma cytokine levels represent only the peak of the iceberg, they are the only way to demonstrate the effectiveness of CVVH.

In all studies in the literature on cytokine elimination in MOSF by various methods of hemopurification, renal failure was a basic requirement for inclusion in those studies [1, 11, 12, 22]. In contrast, none of our patients had renal failure at the beginning of CVVH.

Possibly the most important benefit of continuous methods of blood purification is the improved removal of metabolic waste products and humoral mediators [1, 11, 12, 22]. Technically, CVVH is a highly favored method for removing cytokines because of the use of pure convection [21]. Moreover, tissue oxygenation can be improved by blood purification, and improved tissue oxygenation may be a result of better microcirculation or the removal of mediators [12].

The excessive uncontrolled activation of inflammatory cells and mediators after trauma and major surgery may play a key role in the development of ARDS, MOSF, and the subsequent death of patients [6, 15]. Whereas clinical diagnostic criteria are more helpful in identifying patients with an unfavorable outcome of ARDS [24, 25], the degree of inflammatory response at the onset and during the course of ARDS is strongly related to patient survival [6, 15, 25]. These data support the use of blood purification to eliminate noxious cytokines [1, 11, 12, 22]. Our patients sucessfully underwent CVVH for elimination of IL-6 and IL-8, which correlated with clinical improvement.

All patients in the present study survived. Not only a systemic inflammatory response but an initial exaggerated pulmonary inflammatory response quantified by inflammatory cytokines in the bronchoalveolar lavage fluid are associated with an unfavorable outcome for those with ARDS [26]. By removing major inflammatory mediators, other authors [4, 27–29] and our team were able to improve not only oxygenation but also hemodynamics. A circulating myocardial depressant may be the cause of the myocardial depression that frequently accompanies septic shock. This substance(s) may be eliminated by means of blood purification [30–32].

Two patients in the control group died, and the stay in the ICU was significantly longer for control patients regardless of comparable severity of disease in the patients who survived ($p < 0.05$). We conclude that the elimination of cytokines and several mediators achieved by means of CVVH may improve cardiopulmonary function in critically ill patients.

Résumé

L'activation non-contrôlée des cellules et des médiateurs inflammatoires suite aux traumatismes joue un rôle majeur dans le développement du syndrome de détresse de l'adulte (SDRA) et le syndrome de défaillance multiviscérale (SDM). On a démontré que l'évolution de ces patients était d'autant plus défavorable que le niveau de cytokines était élevé. Cependant, les résultats concernant l'amélioration clinique du SDRA par l'extraction des cytokines circulantes par différentes méthodes d'hémofiltration sont divergents. Sept patients ayant eu un traumatisme ou une chirurgie majeure ont eu une hémofiltration veno-veineuse continue (HVVC) pour traiter leur défaillance cardio-pulmonaire (score de Murray de 2.74), mais pas pour leur défaillance rénale ou hépatique. Le niveau de cytokines a été mesuré au début et à 15, 60, 120 et 240 min après le début de la CVVH (point de mesure MP1-5). On a évaluée l'amélioration clinique ainsi que la corrélation avec les niveaux du taux des cytokines pendant le traitement. Le taux de TNF-α dans le sang artériel a augmenté de 11.14 ng/ml à 17.86 ng/ml ($p < .05$). Les niveaux d'IL-6 ont significativement abaissé pendant la HVVC de 1284.7 ng/ml à 557.9 ng/ml et les niveaux d'IL-8 ont abaissé simultanément d'un niveau initial de 154.4 ng/ml à MP3 à 97.3 ng/ml à MP5. L'amélioration clinique était parallèle à la chute des niveaux sériques d'IL-6 et d'IL-8. Après 2 heures d'HVVC, la situation hémodynamique s'est améliorée de façon significative, comme en témoignaient la diminution de la consommation en catécholamines, une amélioration des pressions artérielles et la diminution des pressions dans l'artère pulmonaire. Deux heures après le début de l'HVVC, l'indexe d'oxygénation a augmenté de façon significative, corrélée à la chute de l'effet shunt. Le score de Murray a diminué de façon significative à 1.86. L'épuration d'IL-6 et d'IL-8 par l'HCCV après la stimulation initiale est corrélée avec l'amélioration clinique, ce qui a été démontré par une meilleure oxygénation et hémodynamique deux heures après le début de l'HCCV. Cependant, l'élimination des cytokines et des médiateurs par l'HCCV peut contribuer à l'amélioration cardiopulmonaire des patients gravement atteints. En comparaison avec le groupe de contrôle ($n = 7$), comparable en termes de syndrome de défaillance multiple, l'amélioration de la défaillance cardiopulmonaire était similaire, et deux de ces patients sont décédés. Le séjour en soins intensifs était plus long pour les patients dans le groupe contrôle.

Resumen

La excesiva e incontrolada activación de células inflamatorias y mediadores después de trauma o cirugía mayor juega un papel clave en el desarrollo del SDRA y la FOMS. Se ha demostrado que los niveles elevados de citocinas afectan en forma adversa la evolución clínica en estos pacientes. Sin embargo, se registran resultados contradictorios con la remoción de las citocinas circulantes mediante diversos métodos de hemopurificación destinados a mejorar la evolución clínica de la FOMS. Siete pacientes que habían sufrido trauma o cirugía mayor fueron sometidos a hemofiltración veno-venosa continua (FVVC) como tratamiento de falla orgánica severa del corazón y pulmones (índice de Murray 2.74), pero no del riñón o del hígado. Se determinaron los niveles de citocinas al comienzo y a los 15, 60, 120 y 240 minutos después de la FVVC (punto de medición MP1-5). Se monitorizó mejoría clínica para correlacionarla con los niveles de citocinas. El nivel arterial de FNT-alpha ascendió de 11.14 ng/ml a 17.86 ng/ml ($p < .05$). Los niveles arteriales de IL-6 disminuyeron en forma significativa en el curso de la FVVC de 1284.7 ng/ml a 557.9 ng/ml y los de IL-8 disminuyeron simultáneamente de un pico inicial hasta de 154.4 ng/ml a MP3 a 97.3 ng/ml a MP5. El descenso en los niveles de IL-6 apareció íntimamente correlacionado con la majoría clínica. A las 2 horas de FVVC la situación hemodinámica mejoró significativamente a juzgar por una disminución en el gasto catecolamínico, un incremento en las presiones arteriales y disminución en las presiones en la arteria pulmonar. Además, a las 2 horas del inicio de la FVVC el índice de oxigenación ascendió en forma significativa, con buena correlación con el descenso en la fracción de shunt. El score de Murray bajó significativamente a

1.86. La remoción de IL-6 e IL-8 mediante FVVC luego de la estimulación inicial se correlaciona con la mejoría clínica, lo cual se demuestra por una mejoría significativa de la oxigenación y de la hemodinámica a partir de las 2 horas del inicio de la FVVC. Sin embargo, la eliminación de las citocinas y de algunos mediadores por la FVVC puede contribuir a la mejoría cardiopulmonar de pacientes en estado crítico. En comparación con el grupo control de pacientes (n = 7) que era similar en términos de la FOMS, ningún tipo de intervención resultó en una mejoría similar de la falla cardio-respiratoria y 2 de estos pacientes murieron. Por lo demás, los pacientes del grupo control tuvieron una permanencia significativamente más prolongada en la UCI.

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Invited Commentary

Charles E. Wiles III, M.D.

Department of Critical Care, Shock Trauma Center, Baltimore, Maryland, USA

The authors present another argument in a series advocating continuous hemodiafiltration for the treatment of multiple organ dysfunction syndrome (MODS). Their results from a small series of patients are impressive. The explanation offered for this success is logical but could benefit from additional objective support.

Three decades of research into the host defenses of the human organism has produced an impressive and increasingly comprehensive understanding of the inflammatory response. The hypothesis that MODS is the product of the systemic inflammatory response gone wild has also emerged. As the details of this process were elucidated, the seductive temptation to intervene pharmacologically and to manipulate host defenses with one or two genetically engineered antibodies to specific mediators became irresistible. To date, however, all trials of antiinflammatory agents to control or cure MODS have been remarkable for their extremely modest success [1, 2].

A broad nonspecific attack on unregulated inflammation—in effect hitting the reset button on the human machine—is beginning to gain momentum. Therapeutic apheresis is a collective term for a variety of *in vivo* techniques that separate plasma or a cellular component from blood or other body fluids such as thoracic duct lymph. Techniques currently in use include plasmapheresis, plasma exchange, extracorporeal plasma adsorption and immunoadsorption, cytopheresis, hemodialysis, and hemofiltration. The unifying theme of these approaches is to "purify" the patient's blood. One hears echoes of Galen and Hippocrates [3].

Success has been reported for the use of therapeutic apheresis in the treatment of a wide variety of conditions, including sepsis and organ failure. Pulmonary failure, for example, has responded well to continuous diafiltration in both children and adults [4, 5]. The mechanism for the improvement observed is not clear. Although cytokines can be detected in the ultrafiltrate of these patients [6], the cardiopulmonary benefits seen in these patients can also be explained by the removal of excess fluid.

The present paper presents a small series of patients. Cytokines were measured in the blood of the study group but not apparently in the control group. Cytokine clearance in the hemofiltrate was not noted.

One hopes the authors will pursue their investigations and provide us with further support for a promising treatment for organ failure that has been characterized as a development in critical care equivalent to mechanical ventilation [7]. Medicine moves in cycles. Perhaps this is the rebirth of the humoral theory of disease.

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