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Blood Purification for Prevention and Treatment of Multiple Organ Failure

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Abstract. Blood purification has been applied conventionally as an artificial kidney or artificial liver in the management of patients with multiple organ failure (MOF), and most blood purifications have been performed intermittently. Recent advances in medical engineering made it possible to perform such blood purifications continuously (i.e., 24 hours a day, 7 days a week if necessary) even in critically ill patients. This modality is referred to as continuous renal replacement therapy (CRRT) or continuous blood purification (CBP). Among many kinds of CBP, continuous hemodiafiltration (CHDF) is most useful for management of MOF, as it can be performed without serious or hazardous side effects, and improvement can be expected with it. Recently, CHDF and polymyxin B immobilized endotoxin adsorption columns were used for the prevention or treatment of MOF, with the expectation that such therapy can be effective as a countermeasure against the pathophysiologic causes of MOF. Our data and that of others clearly indicate that continuous blood purification, such as with CHDF and endotoxin adsorption, can remove or decrease the blood levels of humoral mediators, including proinflammatory cytokines, and can improve tissue oxygenation, especially oxygen consumption (VO_2) among critically ill patients including those with MOF. Blood purification is also useful in the careful management of fluid, electrolytes, and acid-base balance and for the removal of metabolic wastes. Blood purification is now considered to be one of the basic therapeutic tools of critical care, equal to nutritional support with total parenteral nutrition and respiratory support without a ventilator.

Multiple organ failure (MOF) is still associated with high mortality despite advances in understanding its pathophysiology and in modern critical care [1]. Blood purification has been widely applied to patients with MOF as an artificial support such as an artificial kidney or an artificial liver [2]. Recent advances in medical engineering made it possible to apply blood purification continuously (i.e., 24 hours a day, 7 days a week, if necessary) even to critically ill patients, such as MOF patients with renal and hepatic failure [3]. Those methods of blood purification have been referred to as continuous renal replacement therapy (CRRT) or continuous blood purification (CBP) [3]. Recently this therapy has been applied to patients with MOF, with the expectation that it would be as effective as an artificial kidney or artificial liver and that blood purification could help treat or prevent MOF [4]. The present paper reviews the efficacy of CBP such as continuous hemodiafiltration (CHDF) [4] and direct hemoperfusion with endotoxin adsorption columns [5] for prevention or treatment of MOF.

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Technical Consideration

Continuous blood purification is the method of choice for treatment of critically ill patients, such as those with MOF, in the intensive care unit (ICU). CBP has less hazardous side effects than conventional intermittent hemodialysis in patients who are hemodynamically unstable. Reeves and Butt reported that CBP can be performed safely even in critically ill children [6]. Furthermore, it can remove substances with a large extravascular pool more effectively and continuously than the intermittent therapy [3, 4]. Among the various CBP techniques, CHDF is most popular because it can be performed without difficulty, even by a staff unfamiliar with blood purification techniques. Also, it can effectively remove substances with a wide range of molecular weights up to 30,000 to 40,000 daltons [2]. CHDF is a combination of continuous hemofiltration (CHF) and continuous hemodialysis with small-volume dialysate flow. Therefore CHDF is also referred to as continuous hemodialysis with sequential hemofiltration [7]. The flow diagram for CHDF is shown in Figure 1.

The bleeding tendency during CBP caused by prolonged administration of anticoagulant has been a serious problem and one of the reasons this modality has not been more popular in many ICUs [8]. This problem has now been overcome with the use of a new synthetic protease inhibitor with anticoagulating properties, nafamostat mesilate [9]. With this new anticoagulant, the incidence of bleeding complications during CBP decreased dramatically from 67% to 4% in the ICU at our institution [9].

The endotoxin-adsorbing column is a blood purifier that contains chemically immobilized polymyxin B fibers. It effectively removes endotoxin from blood and can be applied as a method of direct hemoperfusion [5]. The flow diagram of direct hemoperfusion with the endotoxin-adsorbing column is also shown in Figure 1.

Removal of Humoral Mediators with CBP

It has been claimed that cytokines, especially proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin 1 (IL-1), play a key role in the pathophysiology of MOF [1, 10]. Therefore if a technique can effectively remove cytokines from the bloodstream, it should be an effective therapy to prevent or treat MOF. Bellomo et al. reported that CHF can remove cytokines

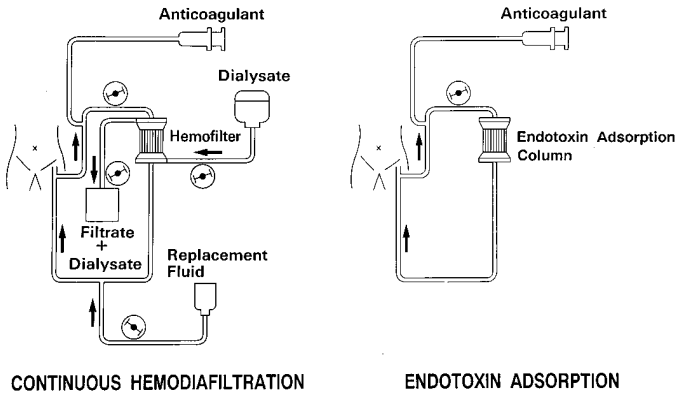

Fig. 1. CHF and endotoxin adsorption with polymyxin B-immobilized endotoxin adsorption column.

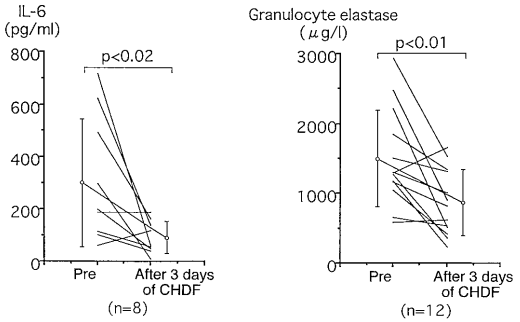

Fig. 2. Changes in blood levels of interleukin 6 (IL-6) and granulocyte elastaste with 3 days of CHDF in patients with MOF. Vertical bars indicate mean ± standard error.

from the circulation of septic patients [11], but their report was recently challenged [12]. They reported that the characteristics (molecular weight, binding kinetics of production, endogenous clearance) of the proinflammatory cytokines TNF and IL-1 were not compatible with clinically important removal by hemofiltration, and that no clinical study showed a reduction in cytokine levels with hemofiltration [10]. Furthermore, it has been pointed out that blood purification can even increase the blood level of the cytokines and other humoral mediators because leukocytes may be activated and release cytokines and other humoral mediators when they pass through the fibers of the hemofilter [12]. However, our study shows that clearance of the cytokines is significant enough to achieve their clinically important removal [4]. It also indicates that clearance of cytokines is especially large when the pretreatment blood levels of the cytokines are high.

Clearances of TNF, IL-1, and IL-6 are at 11.6, 10.6, and 10.4 ml/min, respectively, with our standard procedure of CHDF. However, clearance of granulocyte elastase is negative, indicating that this humoral mediator cannot be removed with CHDF. This condition is acceptable because whether a substance can be removed with blood purification depends on its molecular weight. The molecular weight of granulocyte elastase is reported to be between 50,000 and 100,000 daltons after being combined with α-$_1$-antitrypsin. The hemofilter used in CHDF in our institution can remove only substances with a molecular weight $<$30,000 to 40,000 daltons.

Figure 2 shows the changes in blood levels of IL-6 and granulocyte elastase in patients with MOF treated with CHDF for 3 days continuously. The blood level of IL-6 decreased significantly after 3 days of CHDF treatment. The amount of decrease is especially large when the pre-CHDF level of IL-6 is higher. More interestingly, the blood levels of granulocyte elastase also decreased with 3 days of CHDF, even though the clearance indicated that this mediator cannot be removed with CHDF. Improvement of the patients' condition may be an explanation for the decrease in the blood level of granulocyte elastase. However, clearance of the cytokines and changes in the blood level of cytokines strongly suggest that the decrease in granulocyte elastase is due to a decrease in activation of the cytokine network. It eventually results in a decrease in priming of granulocytes and in the production of granulocyte elastase. We also observed that the oxygenation index improved significantly in patients with septic adult respiratory distress syndrome shortly after beginning CHDF and before the water balance changed, suggesting that some humoral mediators were removed by the CHDF.

The difference between the results cited by Schetz et al. [12] and ours is at least partially explained by the fact that Schetz et al. used CHF whereas our results are with CHDF. CHDF can remove substances more effectively and with larger molecular weights than can CHF [4].

On the other hand, it has been pointed out that complete inactivation of the proinflammatory cytokines with a monoclonal antibody to the cytokines increased the mortality of septic rats. Thus complete inactivation or elimination of cytokines from the bloodstream might be harmful [10]. As seen in Figure 2, the blood level of cytokines, after their removal with CHDF, is not zero, indicating that CHDF can remove the excess cytokines from the blood, leaving a small amount, which may be essential for the patient. Thus removal of cytokines with CHDF is a reasonable countermeasure against hypercytokinemia causing MOF.

Improved Tissue Oxygenation Metabolism with CHDF

Derangement in tissue oxygen metabolism is reported to be an important pathophysiologic factor in the development of septic MOF [1, 13]. It has been proposed that supranormalization of oxygen delivery (DO_2) would be effective in the treatment of impaired tissue oxygen metabolism in the critically ill [13]. A recent study, however, indicated that in septic patients oxygen utilization (VO_2) is not always improved with an increase in DO_2, which can be relatively easily achieved with the increase in cardiac output due to catecholamine administration [13]. CHDF effectively improves VO_2 in septic patients, as shown in Figure 3. In the study whose results are shown in Figure 3, the patients with septic shock in the ICU were divided into two groups. One group was treated with fluid resuscitation and catecholamines and the other group with CHDF in addition to fluid resuscitation and catecholamines, regardless of the patients' renal function, aiming at the removal of humoral mediators. The DO_2 and VO_2 were then compared for the two groups. There was no significant difference in DO_2, but the VO_2 was significantly better in the group treated with CHDF plus fluid resuscitation and catecholamine. This improvement in VO_2 with CHDF might be due to the removal of interstitial edema, with improvement in the microcirculation and uptake of oxygen by parenchymal cells, or it might be due to removal of humoral mediators that depress oxygen uptake by

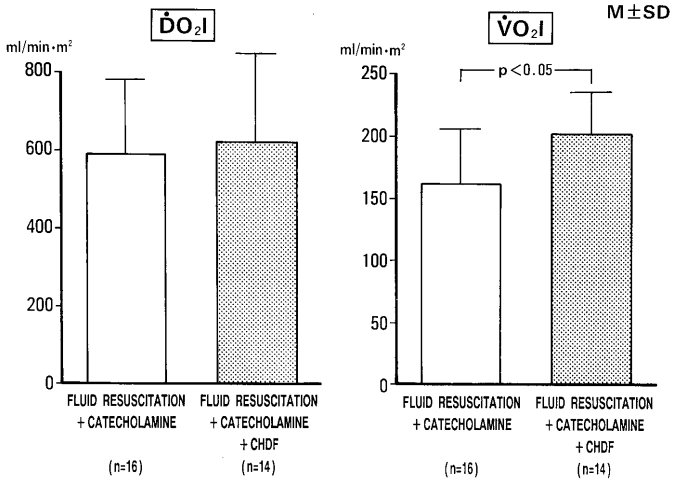

Fig. 3. Comparison of oxygen delivery index (DO_2I) and oxygen consumption index (VO_2I) after fluid resuscitation and catecholamine with or without continuous hemodiafiltration.

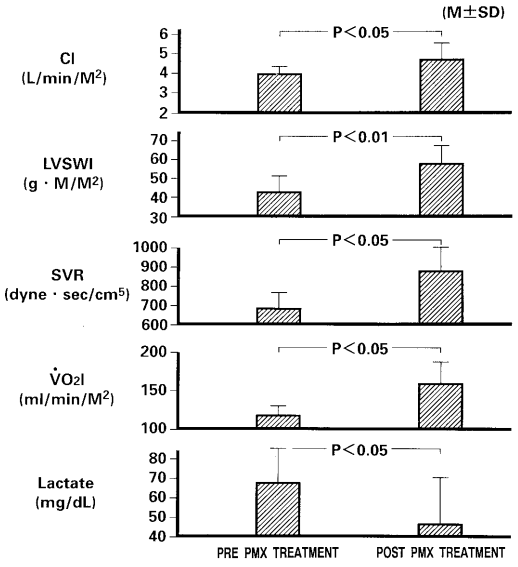

Fig. 4. Changes in hemodynamic and metabolic parameters with endotoxin adsorption with poymyxin B-immobilized adsorption column (PMX).

parenchymal cells. The results in Figure 3 clearly indicate that CHDF can effectively improve tissue oxygen metabolism [13].

Endotoxin Removal

Endotoxin has been claimed to be an important pathogenic factor for sepsis and septic MOF. Many countermeasures against endotoxin have been applied experimentally and clinically with limited efficacy. Polymyxin B-immobilized endotoxin-adsorbing fiber has been clinically available in Japan and has been widely applied to remove endotoxin from the bloodstream of patients. Such blood purification can be performed by direct hemoperfusion. Figure 4 shows the changes in metabolic and hemodynamic parameters after 2 hours of direct hemoperfusion with an endotoxin-adsorbing column. The cardiac index increased despite an increase in systemic vascular resistance, and left ventricular stroke work index was improved. Thus a hyperdynamic circulation with decreased systemic vascular resistance is improved with endotoxin adsorption. The blood lactate levels decreased at the same time the VO_2 increased, indicating an improvement in tissue oxygen metabolism.

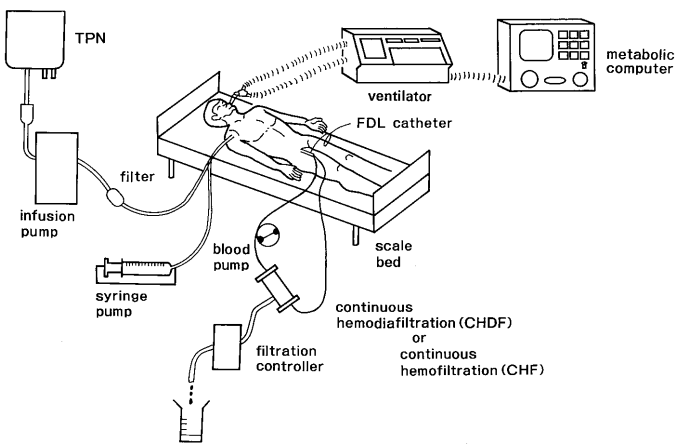

Fig. 5. Method of nutritional support for patients with anuric MOF.

Improvement in hemodynamic and metabolic parameters with endotoxin adsorption might be due to a decrease in the blood level of humoral mediators, caused by decreased activation of inflammatory cells with endotoxin [5]. Therefore endotoxin adsorption with polymyxin B-immobilized columns can be a useful therapeutic tool for endotoxemia and sepsis, for which there are no specific, effective countermeasures in clinical settings.

CHDF for Nutritional Management

Nutritional support is one of the most important therapeutic aspects for the survival of patients with MOF. It is difficult for several reasons to supply a sufficient amount of energy for patients with MOF who are hypermetabolic. Limitation of the infusion volume is one of the most serious limiting factors, as at our institution roughly two-thirds of these patients develop renal failure as a part of MOF [14]. For those patients, CHF or CHDF is required to remove the excess water given as a carrier of total parenteral nutrition (TPN) (Fig. 5). The required ratio of energy intake (energy intake/measured energy expenditure) among patients with MOF receiving TPN was 73.3 ± 14.7% without simultaneous CHF or CHDF. With simultaneous CHF or CHDF, it was 111.2 ± 16.3% ($p < 0.05$). Thus even nutritional support was significantly improved with the application of CHF or CHDF in patients with MOF [14].

Efficacy of Blood Purification

Blood purification is effective in many therapeutic aspects for patients with MOF. Efficacy includes removal of causative substances such as humoral mediators, improvement in tissue oxygen metabolism especially VO_2, exact management of fluid, electrolytes, and acid-base balance, removal of metabolic wastes, proper nutritional support through removal of excess carrier water,

Table 1. Efficacy of blood purification for prevention and treatment of multiple organ failure and the choice of blood purification.

Purpose	Target of purification
Removal of causative substances such as humoral mediators and endotoxin	CHF, CHDF, PMX, CPE, HA
Improvement in tissue oxygen metabolism	CHF, CHDF, PMX
Tight management of fluid, electrolytes, and acid-base balance	CHF, CHDF
Removal of metabolic wastes	CHF, CHDF, CPE
Proper nutritional support by removal of excess carrier water	CHF, CHDF
Improvement of respiratory function by removal of pulmonary interstitial edema	CHF, CHDF
Replacement of essential substances	CPE
As artificial kidney	CHDF
As artificial liver	CPE

CHF: continuous hemofiltration; CHDF: continuous hemodiafiltration; CPE: continuous plasma exchange; PMX: polymyxin B-immobilized endotoxin adsorption column; HA: hemoadsorption.

improvement in respiratory function through removal of pulmonary interstitial edema, and replacement of essential substances that might be depleted in patients with MOF. Blood purification is also effective as an artificial kidney and artificial liver in MOF patients who often develop renal and hepatic failure. As shown in Table 1, the greatest efficacy can be achieved with CHF or CHDF. However, endotoxin adsorption with polymyxin B-immobilized endotoxin adsorption columns is necessary for endotoxin adsorption, and continuous plasma exchange is needed—as an artificial liver and for replacement of essential substances. Hemoadsorption might be necessary for removal of some causative substances. There are many reports on the efficacy of blood purification, especially CBP, for management of patients with MOF [3, 4, 6, 7, 11, 15]. Among the various techniques, CHDF is preferable for management of MOF, as it can be performed without difficulty by a staff who are not familiar with blood purification techniques. Most of the effects listed in Table 1 can be better achieved with CHDF than with CHF [4, 15].

Conventionally, blood purification is performed by the staff of the dialysis center, and usually they are called when blood purification is necessary in the surgical ward or the ICU. However, because of advances in modern medical engineering, CBP has become easy to perform. Every critical care physician, including surgeons who are sometimes involved in the management of MOF, must be familiar with blood purification. Blood purification is now one of the basic therapeutic tools in critical care, equal to ventilators and TPN.

Résumé

Dans le syndrome de défaillance polyviscérale (multiple organe failure ou MOF), on peut filtrer (ou purifier) le sang soit par un rein soit par un foie artificiel, le plus souvent de façon intermittente. Depuis des progrès récents, on peut également pratiquer les filtrations en continue (i.e. 24 heures/jour, 7 jours/semaine, s'il le faut), même chez le patient sévèrement atteint. Cette dernière modalité s'appelle également la thérapie de remplacement rénal continu ou la filtration (purification) sanguine continue. Parmi ces dernières, l'hémofiltration est très utile dans le traitement du MOF, puisqu'elle peut être pratiquée sans qu'il y ait d'effets secondaires nocifs et on est en droit d'attendre une amélioration. Récemment, l'hémofiltration combinée avec des colonnes d'absorption d'endotoxine immobilisée par la polymyxine β ont été utilisées pour la prévention et/ou le traitement du MOF dans l'espoir qu'elles soient effectives contre les causes physiopathologiques du MOF. Nos données, comme celles d'autres auteurs, indiquent clairement que la purification continue telle que l'on obtient avec l'hémofiltration et l'absorption des endotoxines peuvent éliminer ou diminuer le niveau de médiateurs humoraux comprenant les cytokines proinflammatoires et peuvent ainsi améliorer l'oxygénation tissulaire, surtout la consommation en oxygène chez les patients sévèrement malades ayant un MOF. L'hémofiltration est utile restaurer la volémie, équilibrer le bilan électrolytique et acidobasique et éliminer les déchets métaboliques. L'hémofiltration est considérée comme un outil thérapeutique important en soins intensifs, équivalente au soutien nutritionnel fourni par l'alimentation parentérale totale et l'assistance respiratoire sans respirateur.

Resumen

La purificaciòn sanguìnea puede ser convencionalmente aplicada en forma de riñòn artificial o de hìgado artificial en el manejo de pacientes con falla orgànica mùltiple (FOM) y la mayorìa de las purificaciones sanguìneas han sido practicadas de manera int ermitente. Sin embargo, los recientes avances en la ingenierìa mèdica han hecho posible realizar tales purificaciones sanguìneas en forma continua (o sea, 24 horas al dìa, 7 dìas a la semana, si necesario), aun en pacientes en estado crìtico. Esta modalid ad se conoce como terapia de reemplazo renal continua (TRRC) o purificaciòn sanguìnea continua (PSC). Entre muchas clases de PSC, la hemodiafiltraciòn continua (HDFC) es la màs ùtil en el manejo de la FOM, puesto que puede ser realizada sin que haya efect os secundarios serios o peligrosos, y se puede esperar mejorìa con su uso. Recientemente se han utilizado la HDFC y las columnas de adsorciòn de endotoxina inmovilizada con polimixina B en la prevenciòn y/o tratamiento de la FOM, con la esperanza de que t al terapia llegue a ser tan efectiva como una contramedida contra las causas fisiopatològicas de la FOM. Nuestros datos, asì como los de otros, indican claramente que la purificaciòn continua de la sangre, tal como la HDFC y la adsorciòn de endotoxina, pu eden remover o disminuir los niveles sanguìneos de mediadores humorales, incluso las citocinas proinflamatorias, y pueden mejorar la oxigenaciòn tisular, especialmente el consumo de oxìgeno (VO2), en los pacientes en estado crìtico, incluyendo aquellos co n FOM. La purificaciòn sanguìnea tambièn es ùtil en el manejo cuidadoso de los lìquidos, electrolitos y equilibrio àcido-base, asì como en la remociòn de desechos metabòlicos. La purificaciòn sanguìnea es actualmente considerada como uno de los instrument os terapèuticos bàsicos en el cuidado crìtico, igual al soporte nutricional con nutriciòn parenteral total y al soporte respiratorio con ventilador.

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