Continuous Hemofiltration/Hemodiafiltration in Critical Care

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Abstract: Continuous hemofiltration and continuous hemodiafiltration (CHF/CHDF) were developed as continuous renal replacement therapy for patients with severe conditions and has come to be widely performed mainly in critical care, taking the place of intermittent hemodialysis. The membrane pore size of a hemofilter used for CHF/CHDF allows passage of substances ranging from 30,000 to 50,000 Da, and the method for solute removal in CHF/CHDF employs the principle of convection, which is advantageous for removing middle- to high-molecular-weight substances. As apheresis therapy to remove pathogenic substances in blood, CHF/CHDF is being investigated for its possible effect on various morbid conditions. It has recently been found that CHF/CHDF removes humoral mediators including cytokines, particularly in severe systemic inflammatory response syndromes such as septic shock and severe acute pancreatitis. CHF/CHDF is thus beginning to be performed for the prevention and treatment of organ dysfunction secondary to septic shock, trauma, or acute pancreatitis. CHF/CHDF is also efficacious as artificial liver support in preventing adverse effects caused by plasma exchange (PE) and for continuous removal of hepatic coma-inducing substances. CHF/CHDF is thus beginning to be performed for the prevention and treatment of organ dysfunction secondary to septic shock, trauma, or acute pancreatitis. CHF/CHDF is effective for various morbid conditions not only as renal replacement therapy, but also as apheresis therapy and is expected to be applied more widely in critical care in the future. Key Words: Adsorption—Artificial liver support—Continuous hemodiafiltration—Continuous hemofiltration—Cytokines—Mediators.

Continuous hemofiltration (CHF) and continuous hemodiafiltration (CHDF) are blood purification methods developed as forms of renal replacement therapy for patients with severe conditions. As it is performed continuously for 24 h in the ICU, it is also called continuous renal replacement therapy (CRRT) and has recently been widely performed mainly in critical care (1,2).

In CHF/CHDF, water and solutes are removed continuously and gradually, using a small hemofilter with a small volume of extracorporeal circulation. As a result, it affects hemodynamics less than conventional intermittent hemodialysis and permits gradual correction of fluid balance, electrolytes, and osmotic pressure. In addition, the membrane pore size of the hemofilter used for CHF/CHDF is larger than that of the dialyzer used for conventional hemodialysis, allowing passage of substances with molecular weights of 30,000 to 50,000 Da. CHF/CHDF employs the principle of convection to remove solutes, which is advantageous for removing middle- to high-molecular-weight substances, and can efficiently remove substances widely distributed or continuously produced in the body because CHF/CHDF is performed for 24 h.

Sepsis has recently been defined as systemic inflammatory response syndrome (SIRS) caused by infection (3). It is believed that inflammatory cytokines excessively produced as a host response to infection or trauma activate various mediator cascades resulting in production of humoral mediators, and that these humoral mediators cause organ failure (4). We previously reported that CHF/CHDF, which is able to remove humoral mediators including cytokines from the blood, was useful for the prevention and treatment of multiple organ failure (MOF) (5–8).

Because so-called immunotherapy against proin-
Inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β, which are the key mediators of septic shock, have been less efficacious than expected (9). CHF/CHDF has been energetically investigated for its possible efficacy as so-called apheresis therapy in removing humoral mediators, including these cytokines, from the blood (10,11). CHF/CHDF has also recently come to be used as artificial liver support (ALS) for fulminant hepatic failure (FHF) to remove hepatic coma-inducing toxins (12). The indications for CHF/CHDF for removal of these pathogenic substances from the blood referred to nonrenal indication and have attracted clinical attention (1,13). In this review, we survey recent findings on CHF/CHDF as apheresis therapy in critical care and present our findings.

TECHNIQUES FOR CHF/CHDF

CHF was first reported by Kramer and colleagues (14) as continuous arteriovenous hemofiltration (CAVH) in 1977. In this method, filtration is performed for 24 h using the arteriovenous (A-V) pressure gradient and a hemofilter with a small priming volume. This method was initially used for the treatment of patients with congestive heart failure and was reported to be effective. Later, it came to be used for the management of patients with acute renal failure (ARF) accompanied by unstable hemodynamics. However, this method, in which the A-V pressure gradient was used, did not provide stable filtration volume in patients with critical condition accompanied by unstable hemodynamics. Thus, a new method was devised to control blood flow with a peristaltic pump with veno-venous circuit, using a flexible double-lumen catheter placed in a central vein. Thus, continuous venovenous hemofiltration (CVVH) has become mainstream therapy (2). In CVVH, the volumes of blood flow and ultrafiltrate are controlled with a pump using a console for exclusive use (2). CAVH and CVVH are generally termed CHF.

CHF, which affects hemodynamics less than intermittent hemodialysis (IHD) and removes water or solutes gradually, is efficient in maintaining homeostasis. In addition, it permits infusion of intravenous fluids as required for treatment without limitation by removing excess water continuously. Thus, it has become possible to fully manage the nutrition in patients with anuria. However, it was difficult to filter large amounts of blood in many cases because the blood flow rate had to be limited in patients with critical condition accompanied by unstable hemodynamics, and the capacity of CHF for removal of metabolites was insufficient. CHDF was therefore developed. In CHDF, the efficiency of removal of low-molecular-weight substances is increased by perfusing the column of the hemofilter with the dialysate and by adding the principle of diffusion. This increased efficiency of removal has made it possible to manage patients with acute renal failure accompanied by unstable hemodynamics with CHDF alone (15).

Figure 1 shows a flow diagram and the conditions for operation of CHDF in our ICU. The dialysate employed is sterile bicarbonate dialysate; the anticoagulant is a protease inhibitor with a short half-life, namely nafamostat mesilate. Introduction of nafamostat mesilate significantly reduced the incidence of hemorrhagic complications caused by long-term administration of an anticoagulant which was the greatest disadvantage of CHF/CHDF. Thus, CHF/CHDF can thus now be performed safely (16).

REMOVAL OF HUMORAL MEDIATORS WITH CHF/CHDF

As mentioned above, the hemofilter used for CHF/CHDF has a large pore size and employs the principle of convection which is advantageous for removing middle- to high-molecular-weight substances. Thus, the hemofilter can remove various pathogenic substances that may cause organ dysfunction, particularly inflammatory mediators, from the blood, and since the 1980s hemofiltration has been investigated in animal experiments (17,18) and in clinical studies (19–22) for its possible use for the treatment of septic shock. Grootendorst and colleagues (17) demonstrated improvement in right ventricular function after high-volume hemofiltration in a swine septic shock model. They presumed that the effect observed was achieved by removal of myocardial depressant substances by CHF. Ronco et al. (19) showed that CHF/CHDF was effective in improving organ function and reducing the incidence of organ failure in patients with septic shock.
and colleagues (18) reported that CHF removed platelet-activating factor. Hoffman and colleagues (20) reported that CHF removed anaphylatoxins such as C3a and C5a.

Bellomo and colleagues (19) first reported a clinical study of the use of CHDF in septic patients with a polyacrylonitrile (AN69) membrane for hemofilter which removed cytokines such as TNF-α and IL-1β from the blood. The molecular weights of cytokines are as follows: TNF-α, 17.5 kDa; IL-1β, 17 kDa; IL-6, 21 kDa; IL-8, 8 kDa; and IL-10, 18.7 kDa (23). Bellomo and colleagues (19) presumed that these cytokines were removed mainly by convection because it was difficult to remove these high-molecular-weight substances by diffusion. Subsequently, CHF was mainly examined for its possible use for the removal of cytokines, and their effects have been discussed in many subsequent reports (6–8,11,21,22). On the other hand, Shetz and colleagues (24) claimed that it was difficult to remove cytokines from blood by CHF because cytokines had high molecular weights and because TNF-α, in particular, was present in the form of a trimer in the blood. They also claimed that only small amounts of cytokines were removed with CHF/CHDF, if at all, compared with endogenous clearance, and that these amounts were not sufficient to decrease blood concentrations.

We reported that CHDF using a hemofilter with a polymethylmethacrylate (PMMA) membrane was able to remove cytokines from the blood, and that blood concentrations of cytokines significantly decreased after CHDF was performed for 3 days (6–8). Figure 2 shows the changes in blood TNF, IL-6, and IL-8 concentrations from the pre- to the posthemofilter point. The concentrations of all cytokines decreased at the exit of the column, showing that cytokines are effectively removed in one pass through the hemofilter. The blood cytokine concentration in the filtrate is low, indicating that mechanisms other than convection and diffusion are involved in removal of these cytokines.

Table 1 shows the clearance of cytokines calculated from the blood concentration compared with blood urea nitrogen (BUN) and creatinine. The clearances of BUN and creatinine, which are mainly removed by diffusion, were stable regardless of their blood concentration. For cytokines, however, clearances were high in patients with high pre-CHDF blood levels and low in patients with low blood levels. These findings indicate that adhesion to the hemofilter membrane, as well as filtration and dialysis, plays a significant role in the removal of cytokines by CHDF using a hemofilter with a PMMA membrane. Clearances of cytokines in patients with high blood levels are not poor compared with those of BUN and creatinine, and it appears that cytokines are effectively removed from the blood by continuous operation. The efficiency of removal of cytokines differs depending on the membrane material. A PMMA membrane was the best when compared with an ethylene vinylalcohol membrane, a polysulfone membrane, and a cellulose diacetate membrane (8).

De Vriese and colleagues (11,25) recently reported that adsorption to a membrane played a significant role in the removal of cytokines using a hemofilter with an AN69 membrane. They also reported that removal was greatest immediately after start and decreased over time, and that removal was enhanced by increasing the volumes of blood flow and filtration. Bellomo and colleagues (26) also recently compared efficiency in removal of mediators by CHF using a hemofilter with an AN69 membrane for different volumes of filtration (1 L/h versus 6 L/h). They reported that efficiency of removal of anaphylatoxins was increased by high-volume hemofiltration, but that there was no significant difference in removal of cytokines between normal-volume hemofiltration and high-volume hemofiltration. These results suggest that adsorption to a hemofilter membrane is involved in the removal of cytokines and agree with our findings. It may thus be necessary to carefully choose membrane material in performing CHF/CHDF to remove cytokines.

The above findings suggest that adsorption to a hemofilter membrane, as well as convection and diffusion, plays a significant role in the removal of cytokines by CHF/CHDF, and that differences in membrane material and operating conditions are
partly responsible for the controversy that exists concerning removal of cytokines by CHF/CHDF.

**CLINICAL EFFICACY OF MEDIATOR REMOVAL WITH CHF/CHDF**

It has been reported that the clinical effects of CHF/CHDF include improvement of respiratory function (27) and hemodynamics (20,21). Many recent reports on the effects of CHF/CHDF in the treatment of septic shock revealed decrease in cardiac output, increase in systemic vascular resistance, increase in blood pressure, and improvement of hypodynamic state and stated that catecholamine infusion could be reduced (21,22,26,28).

We performed CHDF on patients with MOF and reported that blood cytokine levels significantly decreased, and that the respiratory index (RI), tissue oxygen metabolism, and cellular injury score (CIS) (29) improved (6,8). Because the degree of decrease in cytokine blood level and degrees of improvement in RI and CIS significantly correlated with each other, these effects of CHDF using a hemofilter with a PMMA membrane may have been due to removal of mediators, including cytokines.

It has not been clearly determined whether CHF/CHDF performed to remove mediators improves the survival rate for patients with septic shock or MOF. Kellum and colleagues (30) recently compared the survival rate achieved by IHD and that by CRRT in patients with ARF and reported the results of meta-analysis. According to their report, the overall survival rate did not differ between the two groups, but subgroup analysis, which was performed to compare the survival rates in the two groups among patients with similar disease severity, revealed that survival rate was significantly higher in the CRRT group than in the IHD group. In our study as well, although a historical control was used, among patients with mild disease severity, there were no differences between the CHDF group and the group of patients who were not managed with CHDF, but among patients with moderate to severe disease severity the survival rate was significantly higher in the CHDF group (8).

Recently, CHF/CHDF was reported to be clinically useful when performed in the early phase to remove mediators in patients with morbid conditions other than septic shock. Bauer and colleagues (31) reported that CHF performed prophylactically on patients with trauma improved hyperdynamic state following trauma, resulting in significant improvement on tissue oxygen metabolism.

It is now believed that acute pancreatitis is a typical SIRS not caused by infection, and that inflammatory cytokines induced by inflammation of the pancreas cause SIRS, which becomes severe, and thereby causes organ dysfunction (32). We have been performing CHDF using a hemofilter with a PMMA membrane to remove cytokines for patients with severe acute pancreatitis (SAP) from the early phase and have achieved good results.

![Figure 3](image.png)

**TABLE 1. Relationships between clearances of BUN, creatinine, and cytokines during CHDF with a PMMA hemofilter and pre-CHDF blood levels**

<table>
<thead>
<tr>
<th>MW (kDa)</th>
<th>High pre-CHDF blood level group</th>
<th>Low pre-CHDF blood level group</th>
<th>Cut-off values for high and low blood level groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN 60</td>
<td>14.2 ± 2.5 (n = 17)</td>
<td>14.6 ± 2.1 (n = 22)</td>
<td>100 mg/dl</td>
</tr>
<tr>
<td>Cre 116</td>
<td>18.9 ± 7.3 (n = 12)</td>
<td>17.7 ± 7.1 (n = 23)</td>
<td>5 mg/dl</td>
</tr>
<tr>
<td>TNF 17k</td>
<td>17.2 ± 15.2 (n = 18)</td>
<td>5.0 ± 23.7 (n = 5)</td>
<td>10 pg/ml</td>
</tr>
<tr>
<td>IL-6 21k</td>
<td>8.9 ± 9.0 (n = 22)</td>
<td>1.0 ± 24.6 (n = 12)</td>
<td>100 pg/ml</td>
</tr>
<tr>
<td>IL-8 8k</td>
<td>16.6 ± 21.5 (n = 15)</td>
<td>6.1 ± 29.8 (n = 11)</td>
<td>100 pg/ml</td>
</tr>
<tr>
<td>IL-10 18.7k</td>
<td>18.7 ± 21.4 (n = 4)</td>
<td>3.2 ± 27.9 (n = 5)</td>
<td>8 pg/ml</td>
</tr>
</tbody>
</table>

*Mean ± SD.*

The clinical course and the number of days of ICU stay were significantly lower in the early-treated group. The survival rate was 100% in the early-treated group and 83% in the late-treated group, respectively.

The efficacy of CHF for acute pancreatitis has recently been demonstrated in animal experiments as well. Yakebas and colleagues (33) reported that cytokine levels decreased, and that suppressed cellular immunity, so-called immunoparalysis, was improved after CHF in a swine model of acute pancreatitis. These results suggest that CHF/CHDF is effective for the treatment of SAP, and that CHF/CHDF should be started in the early phase to remove cytokines.

**CHF/CHDF IN CRITICAL CARE**

CHF/CHDF as Artificial Liver Support

Fulminant hepatic failure is a serious condition. Liver dysfunction progresses rapidly and patients may fall into hepatic coma and die. The main cause of deaths in the early phase of FHF is cerebral edema, and it is important to perform appropriate ALS to prevent intracranial hypertension. Conventionally, plasma exchange (PE) has been performed as ALS. In PE, plasma is exchanged over a short period of time, as in IHD, using fresh frozen plasma (FFP). The problems with PE implementation in a short period of time include adverse effects by administration of a large amount of FFP such as hypernatremia, metabolic alkalosis, and rapid decrease in colloid osmotic pressure, possibly leading to complications such as increase in intracranial pressure and pulmonary edema. To reduce these adverse effects of PE implementation we have been performing PE plus CHDF, in which PE is performed as slowly as possible over 6 to 8 h and CHDF is simultaneously performed during PE. CHDF is further continued after PE is completed, to remove hepatic coma-inducing substances continuously. We previously reported that the introduction of PE plus CHDF significantly reduced these adverse effects observed when PE was performed alone (12). Further, we have recently been performing high-flow dialysate CHDF (HFCHDF) on patients with severe coma. In HFCHDF, the column is perfused with a dialysate prepared by a personal dialysis console at 300 to 500 ml/min while performing CHDF. HFCHDF has achieved significant improvement in hepatic coma (Fig. 4). Matsubara and colleagues (34) have already reported that hemofiltration was able to efficiently remove middle-molecular-weight hepatic coma-inducing substances, and that hemofiltration is useful for improvement of hepatic coma. CHF/CHDF is also considered useful as ALS for the treatment of FHF.

**CONCLUSIONS**

In this report, we have reviewed the usefulness of CHF/CHDF as apheresis therapy in critical care, focusing on the removal of humoral mediators. CHF/CHDF, which removes various pathogenic substances from the blood, is useful not only as CRRT but also for the treatment of various morbid conditions requiring critical care. Concerning the efficacy of CHF/CHDF in the treatment of septic shock, it seems necessary in the future to demonstrate the efficacy of CHF/CHDF in a randomized controlled trial and to further elucidate the mechanisms of removal of mediators including cytokines, to choose or
develop a membrane appropriate for the removal of mediators, and to investigate the operating conditions required to increase efficiency in the removal of mediators. In Japan, severe acute pancreatitis and fulminant hepatic failure in patients without renal failure are already approved by the health insurance system as nonrenal indications for CHF/CHDF, and further extension of indications is expected in the future.

REFERENCES