Symposium: What can be expected of continuous slow hemodiafiltration
- Performance standards and clinical indications of hemofilters -

Criteria for Treatment with Acute Blood Purification and Selection of Hemofilters

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Introduction

Basic elements of acute blood purification are dialysis, filtration, adsorption and plasma separation. Acute blood purification can be divided into continuous and intermittent modes. This therapy is continuous and should need to be modified at any time depending on the condition of the patient. To this aim, we have developed and clinically applied on-line CHDF[1]. This system allowed us to select an optimum mode of treatment (HD, HF and HDF) depending on the condition of each patient. Furthermore, by modifying the dilution method, the removal pattern could be adjusted as needed. Thus, a system allowing free changes of the volume of substitute fluid and dialysate has been established. However, membrane filter is another factor which determines the removal efficiency.

In intensive care units, hemofilters have been primarily used for CHDF. However, this type of filter was originally developed for use in slow continuous ultrafiltration (SCUF) and no clear-cut standards for its performances are available. At present, CHDF is used not only as a means of renal support therapy but is playing a central role in the treatment of multiple organ failure by removing humoral mediators such as cytokines[2]. The membrane filter for use in CHDF needs to be selected on the basis of the condition of individual patients and the performance criteria should be defined. This paper will discuss the feasibility of removing cytokines with membrane filters and present standards for selection of membrane filters.

Cytokine-removing experiment

Mini-modules made of various hollow fiber membranes were prepared and used for this experiment *in vitro* to calculate the amounts of cytokines adsorbed and filtrated, while excluding the influence of cytokine generation by the filter. A closed circuit model was used. Each module was perfused with plasma (36 ml), obtained through plasma exchange therapy for patients with sepsis, at a plasma flow rate (Qp) of 1.15 ml/min, and filtration was performed at a Qf of 0.15 ml/min. At 1 and 3 hours of perfusion, the filtrate (Cf) was sampled at a point immediately before the filter (Cpi) and a point immediately after the filter (Cpo). IL-6, IL-8 and TNF-α levels in each filtrate were measured by RIA. After 3 hours of perfusion, the amount adsorbed was calculated using the following equation: Amount adsorbed = Total amount at the start - Amount in each sample - Residual amount.

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The hollow fiber module had a membrane area of 25 cm^2. The amount adsorbed was compared among the following membranes: (1) hydrophilic polysulfone membranes BS-U (Toray) and PS-UW (Fresenius), (2) PMMA membranes, i.e., BK-F, BG-U (Toray) and PAN-SF (Asahi Medical).

Table 1 shows the sieving coefficient (SC) of cytokines as well as the simultaneously measured SC of β_2-microglobulin (β_2MG). For each cytokine, SC was highest with BS-U. The SC with BS-U was 0.14 for IL-6, 0.44 for IL-8 and 0.41 for TNF-α. With the other membranes tested, SC was over 0.1 for IL-8 (a cytokine with a relatively small molecular weight), but was close to zero for IL-6 and TNF-α. SC is expected to be low for membranes with higher adsorbing potentials. Therefore, it will be difficult to accurately assess the amount of cytokines removed by highly adsorptive membranes. For such membranes, a combined evaluation of filtration and adsorption should be needed. We therefore calculated and compared the amounts filtrated and adsorbed after 3 hours of perfusion (**Fig. 1**). For the convenience of data processing, Cf was assumed as constant during each one-hour phase of the experiment, such as, the Cf during the second hour of experiment was assumed as a mean of the Cf at 1 hour and 3 hours. IL-8, a cytokine with a small molecular weight (molecular weight of 8,000), showed changes comparatively similar to those of β_2MG: the amount adsorbed was larger with PAN-SF and the amount filtrated was larger with BS-U. IL-6 is a cytokine with a molecular weight of 21,000. The amount of IL-6 adsorbed was larger with PMMA membranes. Among PMMA membranes, BG-U with a uniform pore size showed larger adsorption of IL-6. The amount of IL-6 filtrated was also large with BS-U. The amount of TNF-α adsorbed was similar for all membranes tested. Filtrated TNF-α was observed only by BS-U. Though the molecular weight of TNF-α is 17,000, it bounds to α_2-macroglobulin in circulating blood. Then we had expected that its filtration would be difficult. In fact, however, filtrated TNF-α was seen with BS-U, probably because free TNF-α was present.

These results indicate that PAN membranes are useful in removing IL-8 by adsorption, and that PMMA membranes are useful in removing IL-6 by adsorption. The results also indicate that hydrophilic PS can filtrate all of the 3 cytokines tested. However, since the cytokine-removing capabilities varied depending on the pore size distribution, electrical charges, etc., even when the membrane is made of the same material, it will be essential to select an optimum membrane on the basis of adequate knowledge about the features of individual membranes.

Table 1. Sieving coefficient (SC) of cytokines for various membranes

	IL-6		IL-8		TNFα		β_2MG	
menbrane	1 h	3 h	1 h	3 h	1 h	3 h	1 h	3 h
BS-U	0.14	0.08	0.44	0.41	0.41	0.37	0.75	0.72
PS-UW	0.01	0.01	0.17	0.11	0.12	0.10	0.47	0.34
BK-F	0.07	0.05	0.25	0.27	nd	nd	0.04	0.13
BG-U	0.04	0.09	0.15	0.27	nd	0.12	0.02	0.18
PAN-SF	0.03	0.05	nd	0.42	nd	nd	0.31	0.30

initial concentration (IL-6 : 320 pg/m*l*, IL-8 : 95 pg/m*l*, TNFα : 65 pg/m*l*, β_2MG : 10 μg/m*l*)

Discussion

The indication of continuous blood purification, which was previously used only for slow elimination of excessive water (SCUF), has recently been expanded to apply to CHDF (primarily aimed at removing pathogenic substances). To date, however, no clear-cut standards on the membranes used for this procedure have been established. If the target

substance to be removed is defined, the selection of an optimum membrane will be easier. However, when cytokines serve as targets, it will be difficult to remove all cytokines with a single type of membrane because the molecular weight and the binding partner vary among different cytokines. On the basis of the results of the present study, we may say that filtration and adsorption are major mechanisms for removal of cytokines. To increase the amount of cytokines adsorbed, the use of a filter with a larger membrane area and larger thickness is recommended. For more efficient utilization of the adsorption, filtration needs to be combined. To improve adsorption, it is also essential to increase the polarization on membrane surface by increasing the filtration rate. In this respect, each membrane, even when the membrane was primarily designed for adsorption of cytokines, should have high water permeability. Membranes primarily aimed at filtration should preferably have larger pore sizes and smaller membrane thickness. However, this type of membrane has a limit associated with an increase in albumin leakage. If a membrane with high water permeability is used, internal filtration during HD is also expected to occur.

The current high performance membranes (HPMs) satisfy the requirements mentioned above and are useful as a means of CHDF. In the future, evaluation of HPM in intensive care field is also desirable.

References

1) Kawanishi H: Introduction of on-line CHDF to intensive care and its problems. Intensive & Critical Care Medicine 9: 743-748, 1997

2) Hirasawa H, Matsuda K, Sugai K, et al: Can continuous hemodiafiltration (CHDF) remove cytokines? - Towards establishing non-renal indications. Japanese Society of Intensive Care Medicine 5: 345-355, 1998

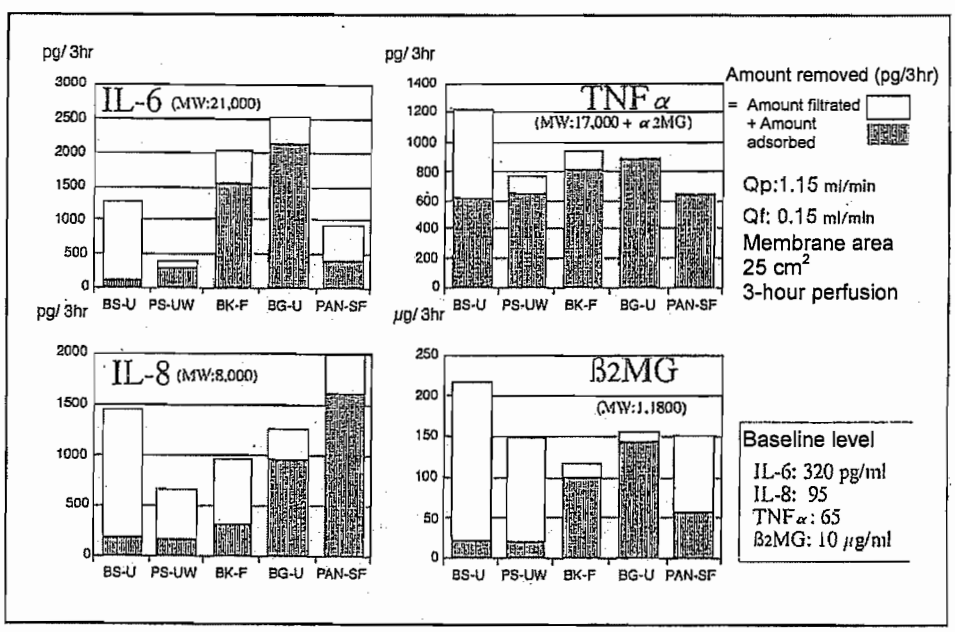

Fig. 1. Removed amounts compared in vitro