

New method of blood purification (Recycle Filtration System)

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Object: We have developed a new blood purification system, the Recycle Filtration System (RFS), because back contamination of endotoxin (ET) from the dialysate in on-line hemodiafiltration (HDF) is a potential problem when a highly permeable membrane is used.

Methods: When the RFS is used for HDF, some of the purified fluid is pumped by a purified fluid pump to the venous side of the blood circuit, and the remainder is returned to the filtrate side of the hemofilter to be used for diffusion. This circuit enables simultaneous diffusion and filtration through the hemofilter.

Results: 1. The rate of removal of urea nitrogen (UN) increased with either decreased or increased quantity of recycled filtration flow (QRF). The rate of removal of beta-2-microglobulin (β 2-MG) decreased as QRF increased, but its clearance and removal rate increased as the quantity of drainage flow increased. 2. No significant change in β 2-MG clearance was observed in the filtration unit, even when recycling was continued for 24 h. 3. ET was not detected in the filtration unit, even though its level in the dialysate, which was reconstituted with tap water, was 806.2 ± 105.4 EU/L.

Conclusion: It is possible to regulate filtration using the RFS by giving importance to the elimination of either small molecules or low-molecular-weight proteins.

Key words: conventional dialysis, endotoxin,, fluid purification, recycle filtration, tap water

INTRODUCTION

Blood purification removes a wide range of substances, from small molecular weight (SMW) substances such as urea nitrogen (UN) to low-molecular-weight (LMW) proteins, such as beta-2-microglobulin (β 2-MG) and myoglobin, by a variety of methods, from hemodialysis (HD) to hemofiltration (HF), hemodiafiltration (HDF), continuous hemofiltration (CHF) and continuous hemodiafiltration (CHDF) (1).

HDF and HF are costly because they require 5-20 L of fluid supplementation and they are also complicated procedures, so to overcome their disadvantages, on-line HDF (2) and push/pull HDF (3) were developed to use the dialysate as a substitution fluid. To increase the clearance of LMW proteins, a highly permeable membrane with a large pore size is used, but there is potential for back contamination of endotoxin (ET) from the dialysate. Therefore, water quality control is essential to ensure that the dialysate has the same quality as injection fluid, and from a safety viewpoint, on-line HDF and push/pull HDF are not recommended for blood purification in the intensive care unit (ICU) or in the home setting.

We have developed a novel purification system, the Recycle Filtration System (RFS), which has the following advantages. 1. It is as safe as using a conventional membrane against ET contamination. 2. It achieves the same level of solute removal as HF or HDF, which use

a highly permeable membrane. 3. Fluid supplementation is not necessary.

In this report, we demonstrate the mechanism of the RFS in both fundamental and clinical experiments, and confirm the clearance of SMW substances and LMW proteins, with no back contamination of ET. We performed RFS on 18 patients under hemodialysis and HF on 10 patients under hemodialysis. Then, the solute removal rate and the safety were evaluated.

SUBJECTS AND METHODS

1 FUNDAMENTAL EXPERIMENT

Circuit diagram of RFS

The RFS comprises a hemofilter and a recycle unit, the latter consisting of a dialysis unit and a filtration unit. Blood is pumped to a hemofilter, a 1.9- m^2 polysulfone F-80 (Fresenius AG, Bad Homburg, Germany), and the filtrate is transported by the recycle pump to the dialysis unit where diffusion against the dialysate achieves electrolyte adjustment and removal of SMW substances such as urea nitrogen (UN) and creatinine (Cr). A 2- m^2 conventional regenerated cellulose dialyser CL-S20*1 (Terumo Corp., Tokyo, Japan) is used in the dialysis unit. After the filtrate from the hemofilter has been treated in the dialysis unit, it is transported by the recycle pump to the filtration unit, which also uses a regenerated cellulose membrane (CL-S20). LMW proteins are concentrated by the filter and a drainage pump drains the concentrate outside the RFS. The

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*1 CL-S20 is a conventional dialyser with ultrafiltration coefficient of 16.8 mL/h/mmHg/2.0 m^2 with bovine blood. Urea and creatinine clearances of 190 and 180 mL/min, respectively, at QB = 200 mL/min QD = 500 mL/min and Qf = 10 mL/min.

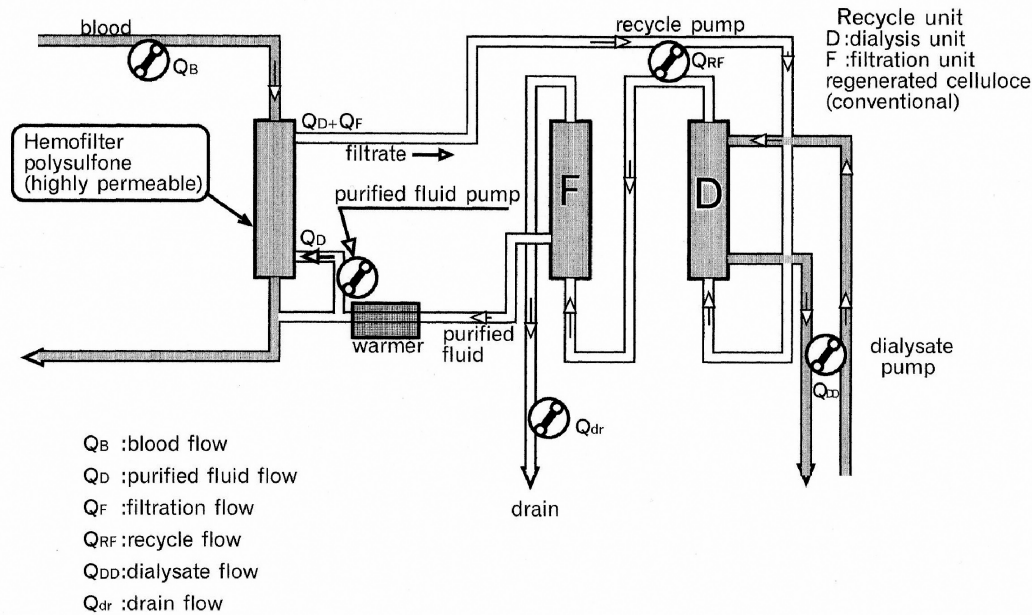


Fig. 1. The Recycle Filtration System (RFS) consists of a hemofilter and a recycle unit, the latter comprising a dialysis unit and a filtration unit. The filtrate from the hemofilter is transported by the recycle pump to the dialysis unit where diffusion against the dialysate achieves electrolyte adjustment and removal of small-molecular-weight substances. After the filtrate from the hemofilter has been treated in the dialysis unit, it is transported to the filtration unit by the recycle pump. Low-molecular-weight proteins are concentrated by the filter and a drainage pump drains the concentrated fluid outside the RFS.

drain flow is set according to the water removal rate required for the patient. By this process, the filtrate from the purified filtration unit, which contains the adjusted electrolyte concentrations, returns to the venous side of the blood circuit. Figure 1 is a circuit diagram of the RFS when it is used for HF or HDF.

When the RFS is used for HDF and CHDF, a purified fluid pump is used and the recycle unit has the same set-up as shown in Figure 1. Some of the purified fluid is pumped to the venous side of the blood circuit, and the remainder is returned to the filtrate side of the hemofilter to be used for diffusion. This circuit enables simultaneous diffusion and filtration in the hemofilter.

EXPERIMENTAL PROTOCOL

1. Solute clearance rates of the recycle unit and its durability

Because the various forms of blood purification therapy use different flow rates, we studied solute clearances over a wide range of flows. The durability of the recycle unit was also examined to assess its applicability for continuous therapy.

(1) Clearance of SMW substances in the dialysis unit

The UN and Cr clearances were monitored using only the circuit of the dialysis unit, which removes SMW substances. The HF drainage fluid was pooled and stirred at room temperature, and the installed circuit was a single-pass system. A 2-m² regenerated cellulose membrane (CL-S20, Terumo Corp.) was

used in the dialysis unit, which was positioned with the recycle entrance port at the lower end. Kindaly No. 2 solution*² (Fuso Pharmaceutical Industries Ltd, Osaka, Japan) diluted 35-fold in tap water and pooled at room temperature was used as the dialysate. The dialysate pump maintained equivalent dialysate flows (QDD) at the inlet (Di) and outlet (Do) ports. To confirm the dependence of clearance on the recycle flow (QRF), QRF was set at 10, 30, 50, 80 and 100 mL/min by the recycle pump. To examine the dependence of clearance on QDD, the QRF: QDD ratio was varied to 1: 1, 1: 1.5, and 1: 2 for each QRF setting.

Sampling was conducted at the Di and Do ports. UN and Cr clearances, and the recycle rate (equivalent to solute clearance efficiency in the HF drainage fluid) were calculated using Equations 1 and 2, respectively, in Table 1.

(2) Clearance of LMW proteins in the filtration unit

The β 2-MG clearance was monitored using only the filtration circuit, which removes LMW proteins. A 2- or 4-m² regenerated cellulose membrane (CL-S20, Terumo Corp.) was used in the filtration unit, which was positioned with the recycle inlet port at the lower end. The QRF was controlled by the recycle pump, and the drainage flow (Qdr) by the drain pump. The filtrate side (recycle fluid side) of the filtration unit was operated as an open system. As a pressure control, the recycle inlet port pressure (Pi) was equal to the outlet port pressure (Po). To confirm the dependence of clearance on the QRF, the Qdr was fixed at

*2 Kindaly No. 2 solution is a type of dialysate. The electrolytes are Na+ 140 mEq/L, K+ 2.0 mEq/L, Ca++ 3.0 mEq/L, Mg++ 1.0 mEq/L, Cl- 110 mEq/L, CH3COO- 8 mEq/L, HCO3- 30 mEq/L.

Table 1

$$CL = \frac{C_{Di}-C_{D0}}{C_{Di}} \times Q_{RF} \quad \dots\dots\text{Eq 1}$$

$$R = \frac{C_{Di}-C_{D0}}{C_{Di}} \times 100 \quad \dots\dots\text{Eq 2}$$

$$CL = \frac{C_{Fi} \times Q_{FR} - C_{FF} \times (Q_{RF} - Q_{dr})}{C_{Fi}} \quad \dots\dots\text{Eq 3}$$

$$R = \frac{C_{Fi} - C_{FF}}{C_{Fi}} \times 100 \quad \dots\dots\text{Eq 4}$$

$$TMP = \frac{P_i + P_0}{2} \quad \dots\dots\text{Eq 5}$$

$$CL = \frac{C_{Bi} \times Q_B - C_{Bo} \times (Q_B - Q_{dr})}{C_{Bi}} \quad \dots\dots\text{Eq 6}$$

$$CL = \frac{R}{100} \times Q_{RF} \quad \dots\dots\text{Eq 7}$$

$$\frac{R}{100} = \frac{\exp\{-NT(Z-1)\}}{\exp\{NT(Z-1)\}-Z} \quad \dots\dots\text{Eq 8}$$

$$NT \equiv \frac{K \times A}{Q_{RF}} \quad Z \equiv \frac{Q_{RF}}{Q_{DD}}$$

Nomenclature

- CL : Clearance
- C_{Di} : inlet concentration at the dialyzer
- C_{D0} : outlet concentration at the dialyzer
- C_{Fi} : inlet concentration at the filtration
- C_{FF} : filtrate concentration at the filtration
- C_{Bi} : inlet concentration at the blood
- C_{Bo} : outlet concentration at the blood
- R : recycle rate
- TMP : transmembrane pressure at the filtration
- P_i : inlet pressure at the filtration
- P_0 : outlet pressure at the filtration
- Q_B : blood flow rate
- Q_{RF} : Recycle flow rate
- Q_{DD} : dialysate flow at the dialyzer
- Q_{dr} : drain flow rate
- K : overall mass transfer coefficient at the dialyzer
- A : membrane area

5 mL/min and QRF was set 10, 30 or 50 mL/min. Because of the ultrafiltration rate, a 2m² membrane was used when the QRF was 10, 30 or 50 mL/min, and a 4m² membrane was used at 80 and 100 mL/min. To confirm the dependence of clearance on Qdr, the experiment was conducted using a 2 m² membrane with the QRF fixed at 50 mL/min, and the Qdr set at 5, 10 or 15 mL/min.

Sampling was conducted at the recycle inlet (Fi) and outlet (FF) ports after the system had stabilized for 1 h. The β2-MG clearance and recycle rate were calculated using Equation 3 and 4, respectively, in Table 1.

(3) 24-h continuous recycle experiment

A 24-h continuous recycle experiment was conducted using only the filtration unit, which has the heaviest load in the RFS. HF drainage fluid was stirred at room temperature and the β2-MG concentration was monitored. Sampling was conducted at 1, 2, 4, 6, 12, 18 and 24 h after circulation started. Clearance was calculated using Equation 3 shown in Table 1. The transmembrane pressure (TMP) was calculated using Equation 5 in Table 1.

2. RFS test with bovine blood

(1) Range of recycle flows used in continuous therapy

The RFS was tested using bovine blood with a total protein (TP) level of 6.6 g/dL and 31% hematocrit (Ht), in a range of recycle fluid flows appropriate for continuous therapy. The UN, Cr, human β2-MG (Sigma Chemical Co., St Louis, MO, USA) and ET concentrations were measured. A 0.6- m² polysulfone membrane (PS-0.6 uw, Fresenius AG) was used in the first filter, and a 2- m² regenerated cellulose membrane (CL-S20, Terumo Corp.) was used in the dialysis and filtration units. After adding UN, Cr and β2-MG, the latter in the form of concentrated HF drainage fluid, to the blood, a 5-L pool was stirred and maintained at 37°C. Blood flow (QB) was set at 100 mL/min. The ratio of the recycled dialysate flow (QD: recycled fluid returning to the filtration side) to the filtration flow (QF) was varied. HF at a QD: QF ratio of 0: 30 mL/min (Fig. 1), and HDF at QD: QF ratios of 10: 20 or 20: 10 mL/min (Fig. 1) were tested. The drainage flow

of the hemofilter (QD+QF) was fixed at 30 mL/min. These conditions were used to study effect of the QD: QF ratio on solute clearance. In the recycle unit, QDD was set at 30 mL/min and Qdr at 5 mL/min.

At the beginning of circulation, only the circulatory system was used, with the dialysate pump turned off. The dialysate pump was started 20 min after the start of circulation, when removal of SMW substances started. At 40 min after the start of circulation, the experimental circuit was switched to the single-pass system and sampling commenced 1 h later. The stabilizing time was 40 min for SMW substances and 1 h for LMW proteins. Sampling was conducted at the blood inlet (Bi) and outlet (Bo) ports. Clearance was calculated using Equation 6 in Table 1.

Sampling for ET measurement was done 4 h after circulation was started, at the dialysate inlet port (Di) and from the recycled fluid (FF).

(2) Range of recycle fluid flows used in maintenance dialysis

The performance of the RFS using bovine blood was tested with a range of recycle fluid flows used in conventional maintenance therapy, and the solute clearances and ET back contamination from the dialysate side were examined using the same parameters as in Experiment 2- (1). After adding UN, Cr and β2-MG to bovine blood (TP 6.5 g/dL, 32% Ht), a 5-L pool was stirred and maintained at 37°C. HF at QB = 210, QD = 0 and QF = 80 mL/min was conducted (Fig. 1). The recycle unit settings were QDD = 130 and Qdr = 5 mL/min.

Experimental procedures, stabilizing times, sampling and clearance calculations were the same as in Experiment 2- (1).

2 CLINICAL APPLICATION

We used the RFS (Fig. 1) in the clinical setting and compared its performance with that of conventional HF. We performed this clinical study 12 years ago. At that time, there was no Institutional Review Board (IRB) . Therefore, the patients gave informed consent to participate in the study, and the investigation was performed in accordance with the principles of the

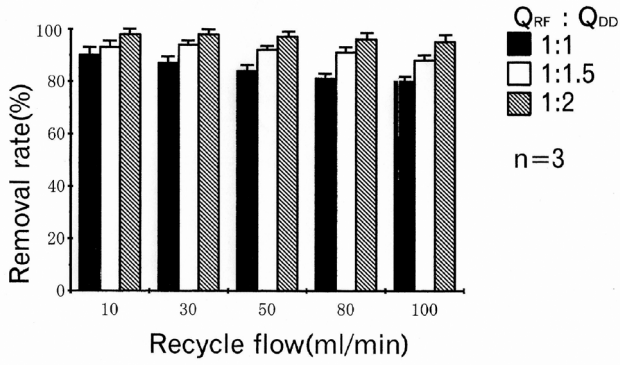


Fig. 2. Removal rate of urea nitrogen (UN) in the dialysis unit of the recycle unit of the Recycle Filtration System (RFS) increased with decreased QRF or increased QRF: QDD ratio, and decreased with increased QRF, or decreased QRF: QDD ratio.

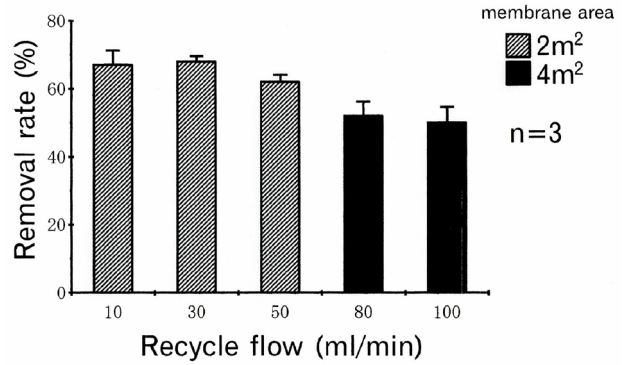


Fig. 3. Removal rate of β 2-MG in the filtration unit of the recycle unit of the Recycle Filtration System (RFS) decreased as QRF increased.

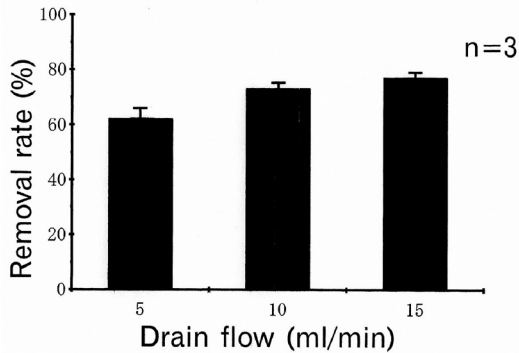


Fig. 4. Clearance and removal rate of β 2-MG in the filtration unit of the recycle unit of the Recycle Filtration System (RFS) clearance increased as Qdr increased.

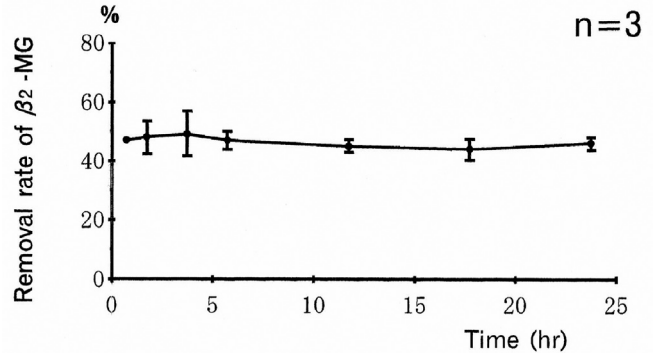


Fig. 5. Change in β 2-MG removal rate over time. No significant change in the clearance was observed in the filtration unit, even when recycling was continued for 24 h.

Declaration of Helsinki.

(1) Subjects

The RFS (HF circuit type, filtrate recycling: 16-24 L, mean 19.8 L) was used for 18 hospitalized patients on maintenance dialysis (14 males, 4 females; mean age 54.1±11.8 years; mean dialysis history 10.8±3.9 years; mean body weight 51.5±9.0 kg). Conventional HF (20 L replacement) was performed in 10 of them.

(2) System

The RFS was set up as shown in Figure 1. The hemofilter was a 1.9- m² polysulfone F-80 (PS-0.6 uw, Fresenius AG) and regenerated cellulose membranes (CL-S20, Terumo Corp.) were used for the recycle, dialysis and filtration units. Two membranes in series were used for the filtration unit in order to obtain a clinically feasible filtration volume. The RFS conditions, such as QRF, QDD, Qdr, were selected in consideration of their effects on solute removal capacity (from the in vitro results) and the predicted therapeutic conditions: QRF = 80 mL/min; QDD = 130 mL/min; Qdr = 5 mL/min. Kindary No. 2 solution was used as the dialysate and 20 L of Sublood B*³ (Fuso Pharmaceutical Industries) was used as the

replacement solution.

(3) Study parameters

The performance and safety of the RFS in the clinical setting were investigated and compared with conventional HF. Blood samples were obtained at the beginning, midway and upon completion of blood purification and the solute removal rates, peripheral blood tests, serum complement values and changes in vital signs recorded.

(4) Statistical analyses

Mann-Whitney's *U* test was used to compare RFS to HF. Difference with P<0.005 was considered significant. The relation between the volume substitution fluid and removal rate was investigated by Pearson's correlation coefficient test.

RESULTS

1 FUNDAMENTAL EXPERIMENT

1. Solute clearance rates of the recycle unit and its durability

(1) Removal of SMW substances

The UN removal rate increased with decreased QRF or increased QRF: QDD ratio, and decreased

*3 Sublood B is a type of supplemental fluid. The electrolytes are Na⁺ 140 mEq/L, K⁺ 2.0 mEq/L, Ca⁺⁺ 3.5 mEq/L, Mg⁺⁺ 1.0 mEq/L, Cl⁻ 111 mEq/L, CH₃COO⁻ 3.5 mEq/L, HCO₃⁻ 35 mEq/L.

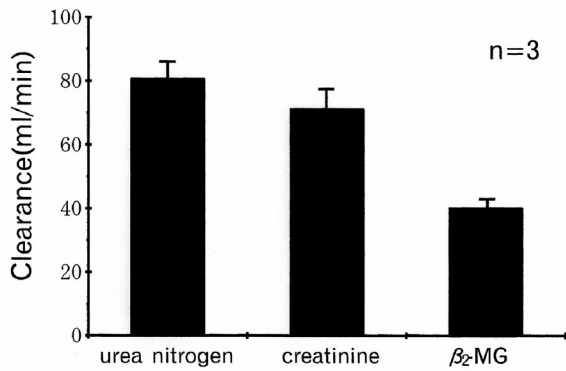


Fig. 6. Solute clearances in the Recycle Filtration System (RFS) tested with bovine blood. The UN clearance was 80.9 ± 1.0 mL/min, Cr clearance was 72.0 ± 2.5 mL/min and β₂-MG clearance was 40.1 ± 0.9 mL/min at QRF = 80 mL/min, QB = 210 mL/min, QF = 80 mL/min, Qdr = 5 mL/min.

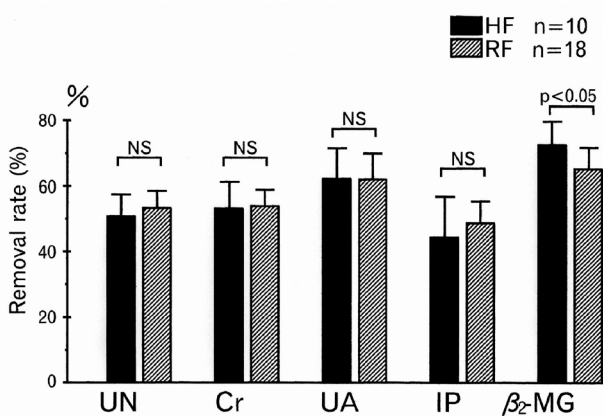


Fig. 7. Comparison of conventional HF with RFS.

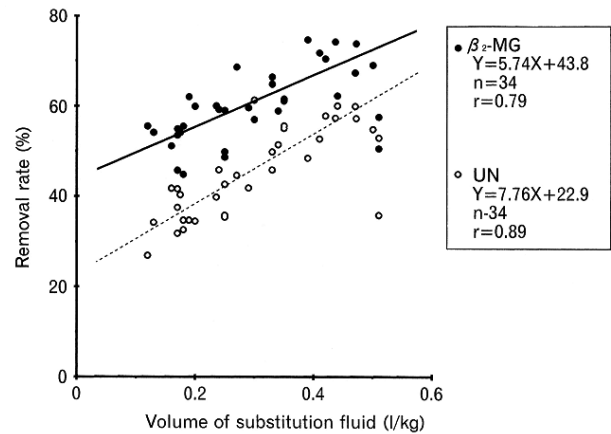


Fig. 8. Confirmation that when using the RFS, an increase in the solute removal rate depends on the recycle fluid volume (total QRF).

with increased QRF or decreased QRF: QDD ratio (Fig. 2).

(2) Removal of LMW proteins

The β₂-MG removal rate decreased as QRF increased. β₂-MG clearance and increased as Qdr increased (Figs 3 and 4).

(3) 24-h continuous recycle experiment

Figure 5 shows the changes in β₂-MG clearance over 24 h, with the average value at 1 h indexed at 100%. No significant change in β₂-MG clearance occurred in the filtration unit, even when recycling was continued for 24 h.

2. RFS test with bovine blood

(1) Range of recycle fluid flows used for maintenance dialysis

As shown in Figure 6, at QRF = 80 mL/min, the UN clearance was 80.9 ± 1.0, Cr clearance was 72.0 ± 2.5 and β₂-MG clearance was 40.1 ± 0.9 mL/min.

(2) ET concentration

ET was not detected in the recycle fluid (detection limit: 0.75 EU/L), even when using a dialysate reconstituted in tap water that contained ET at an average level of 833.1 ± 74.2 EU/L. ET was not detected in the filtration unit, even though the ET level in the dialysate was 806.2 ± 105.4 EU/L.

2 CLINICAL APPLICATION

1. Comparison of RF and HF solute clearance rates

The solute clearance rates with the RFS were as follows: UN: 53.3 ± 5.5%; Cr: 53.9 ± 5.2%; UA: 62.0 ± 8.1%; IP: 48.7 ± 6.9%; and β₂-MG 65.0 ± 6.9%. The

corresponding rates for HF were 49.2 ± 7.2%, 52.2 ± 8.0%, 60.9 ± 8.8%, 42.3 ± 11.2% and 70.9 ± 7.6% (Fig. 7). These data confirmed that when using the RFS, an increase in the solute removal rate depends on the recycle fluid volume (total QRF) (Fig. 8). The removal rates of SMW substances of the RFS are equal to HF (Mann-Whitney method).

2. Changes in other parameters

There were no significant changes in the leukocyte or platelet count in the peripheral blood tests between before starting and upon completion of RFS. No remarkable change in Ht or TP was observed. Electrolyte compensation and acidosis correction were also sufficient. No significant changes in serum complement values were noted. No patients complained of side-effects during or following RFS and there were no clinical side-effects.

DISCUSSION

The performance and durability of a novel blood purification method, the RFS, were confirmed in fundamental and clinical experiments. The dialysis unit, which removes SMW substances, and the filtration unit, which removes LMW proteins, were tested separately and the durability of the filtration unit, which has the heaviest load, was tested in a 24-h continuous recycle experiment.

In the dialysis unit, increased QRF was accompanied by increased UN and Cr clearances, but a

tendency toward a decreased recycle rate, because of clearance as a result of diffusion in the filtration unit, as represented by Equations 7 and 8 in Table 1 (4). Therefore, the SMW substance clearance rate can be improved by increasing the QRF, or by increasing the QRF: QDD ratio if the recycle rate is maintained.

In the filtration unit, increased QRF was accompanied by increased β 2-MG clearance, but a tendency toward a decreased recycle rate. A possible reason is that when the Qdr and membrane area are fixed, increased QRF results in an increased rate of β 2-MG concentration in the hollow-fibers of the filtration unit, causing increased leakage of β 2-MG into the filtrate (recycle fluid) side of the filtration unit. This hypothesis is supported by the observed increases in β 2-MG clearance and recycle rate when the QRF was fixed and the Qdr was increased. Therefore, if Qdr is fixed, a desirable β 2-MG clearance can theoretically be obtained by increasing the QRF. In practice, however, β 2-MG clearance depends on the filtration flow (QF) in the hemofilter, and the different molecule sizes may greatly influence the clearance of LMW proteins from blood. In the 24-h continuous recycle experiment, there was no significant deterioration in β 2-MG clearance with time, despite a high TMP. Recycling for 24 h was possible without a significant decrease in efficiency, suggesting that the RFS is suitable for continuous therapy. The findings also indicate that the recycle unit provides effective clearance and durability for the wide range of recycle flow rates used in continuous therapy and maintenance dialysis.

An in-vitro experiment using bovine blood was conducted using the RFS with a polysulfone membrane and a range of recycle flow rates applicable for continuous therapy and maintenance dialysis. The experiment confirmed the efficiency of solute clearance from blood by the RFS and the safety of the system against ET contamination.

Because β 2-MG removal is highly dependent on filtration, its clearance depends strongly on the QF in the first filter. UN and Cr clearances, which rely mainly on diffusion, depend heavily on the total drainage flow in the first filter ($QRF = QD + QF$). Therefore, in patients in whom an adequate QF cannot be maintained, the QRF can be increased by increasing the QD, until adequate clearance of SMW substances occurs. These findings suggest the usefulness of this system for HDF and CHDF therapies in particular.

Because of the ultrafiltration rate, the regenerated cellulose membrane currently used in the filtration unit of the RFS has a maximum QRF of 100 mL/min, so the UN clearance can be increased up to 100 mL/min by increasing the QD. Maintenance dialysis is possible if the required volume of recycle treatment is obtained. Further studies will be conducted on the differential molecular size and ultrafiltration rate of the membrane to improve clearance of SMW substances and LMW proteins and to enable use of the RFS with even higher flow rates (>100 mL/min).

ET was not detected in the recycle fluid regardless of the QB, QRF and QDD, when the RFS was operated at the levels of performance applicable to continuous therapy and maintenance dialysis. The safety against ET contamination was probably achieved by

two mechanisms. In the dialysis unit, the regenerated cellulose conventional membrane prevents back filtration at low QDD. Moreover, ET has to pass through two layers of conventional filters to gain access from the dialysate to the recycle fluid. Because the conventional membrane of the RFS has the same properties as that used clinically as an ET filter for dialysate, it was not surprising that ET was undetectable in the recycle fluid after more than 4 h of circulation. These results suggest that the RFS is safe from ET contamination when used for continuous therapy.

The RFS, as a means of recycling filtrate used as replacement fluid, was able to efficiently remove SMW substances by diffusion, as well as LMW proteins, such as β 2-MG, by filtration. The β 2-MG removal rate was slightly lower with the RFS than with HF; however, if the Qdr and the membrane area are constant, the rate of leakage of β 2-MG into the hollow-fibers of the filtration unit increases as the QRF increases, which we believe is the reason why the amount of β 2-MG leaking into the recycle solution of the filtration unit increased. The fractional molecular weight used in the filtration unit is a factor related to the removal of LMW proteins, so it is desirable in the future to improve the efficiency of the filtration rate and/or decrease the value of the fractional molecular weight of the membrane. There were no striking changes before or after RF for the removal of TP or Ht etc. and we believe that water removal was adequate. There were no significant differences in the peripheral blood tests and serum complement values, and therefore the biological compatibility of the system is thought to be adequate. Based on these findings, we conclude that clinical application of the RFS is a realistic possibility. The RFS does not require special management of the dialysis fluid, so can be used not only for the treatment of chronic renal failure, but also for home dialysis and in the ICU for acute renal failure or multiple organ failure. Furthermore, it is possible to choose between giving importance to the elimination of either SMW molecules or LMW proteins depending on whether the recycle fluid in HDF is used as a dialysis fluid or as fluid supplementation.

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