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Effects of Reduced Dialysis Fluid Flow in Hemodialysis

Tetsuya Kashiwagi[1,5], Kazuto Sato[2], Seiko Kawakami[2], Masayoshi Kiyomoto[2], Miho Enomoto[3], Tatsuya Suzuki[4], Hirokazu Genei[4], Hiroaki Nakada[4], Yasuhiko Iino[1] and Yasuo Katayama[1]

[1]Division of Neurology, Nephrology, and Rheumatology, Department of Internal Medicine, Nippon Medical School
[2]Adachi Iriya Toneri Clinic, Tokyo
[3]Ayase Kidney Clinic, Tokyo
[4]Kitasenju East Kidney Clinic, Tokyo
[5]Hakusaido Medical Institute, Tokyo

Abstract

Background: Hemodialysis is a treatment in which uremic toxins and excess water content are removed from the blood with a dialyzer and dialysis fluid. The efficiency of hemodialysis is strongly influenced by the following 3 parameters: the blood flow rate (Q_B), the dialysis fluid flow rate (Q_D), and the overall mass transfer area coefficient (K_0A), an index of a dialyzer's performance. The flow ratio (Q_B : Q_D) to obtain a well-balanced dialysis efficiency is generally said to be 1 : 2. In Japan, the Q_B is controlled independently (from 200 to 250 mL/min) depending on individual conditions. However, the Q_D is usually set at around 500 mL/min regardless of the Q_B.

Materials and Methods: To investigate the effect on dialysis efficiency of decreasing the Q_D from 500 to 400 mL/min, 12 patients were divided into two groups: one in which the Q_B was 150 mL/min, with 1.3-m^2 membranes; and another in which the Q_B was 200 mL/min, with 1.6-m^2 membranes. We defined the conditions with the Q_D of 500 mL/min as condition A, and that with the Q_D of 400 mL/min as condition B. Each operating condition was assigned for 2 weeks as crossover trials. To evaluate solute removal, we calculated clearance, reduction rate, removal amount, clear space, the clear space rate, and albumin leakage. Furthermore, when dialysis efficiency decreased in condition B, we performed a supplementary test: we calculated the Q_B with the K_0A equation to achieve a dialysis efficiency equivalent to that in condition A, defined as condition B', as the operating condition with the calculated Q_B and a Q_D of 400 mL/min, and re-evaluated.

Results: In condition B, a Q_B of 150 mL/min had no effect on the dialysis efficiency; whereas with a Q_B of 200 mL/min, slight yet significant differences were observed in the clearance of small molecular weight solutes. Condition B' (Q_B=210 mL/min) showed an equivalent or greater dialysis efficiency and demonstrated an association with theoretical values.

Conclusions: In hemodialysis, the flow ratio (Q_B : Q_D) should be maintained at 1 : 2 to obtain a well-balanced dialysis efficiency. The present study has shown that the Q_D can be decreased while maintaining this flow ratio. A well-balanced Q_D setting can be financially and environmentally conscious. In addition, use of the K_0A equation is a highly effective method to calculate a Q_B that allows an expected dialysis efficiency to be achieved in case the Q_D needs to be decreased uniformly, as when dialysis fluid is in short supply during times of disaster.
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Key words: hemodialysis, blood flow, dialysis fluid flow, dialysis efficiency, blood and dialysis fluid flow ratio

Correspondence to Tetsuya Kashiwagi, Divisions of Neurology, Nephrology, and Rheumatology, Department of Internal Medicine, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: tk@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

Introduction

Hemodialysis (HD) is a treatment to remove useless solutes (e.g., uremic toxins) from the blood to regulate electrolyte concentrations and to remove excessive water content. In HD, the blood is brought into contact with dialysis fluid through semipermeable membranes in a dialyzer. In terms of the solute removal principle, diffusion is used for small molecular weight (Mw) solutes, and ultrafiltration is used for large-Mw solutes; using the concentration gradient, the flows of blood and dialysis fluid are countercurrent to maximize the diffusion transfer efficiency. The blood flow rate to a dialyzer is generally expressed as "Q_B," and the dialysis fluid flow rate to a dialyzer as "Q_D"; both Q_B and Q_D are expressed in volume flow rate (mL/min). The Q_B and Q_D are important factors that influence solute removal during HD[1–3]. In Japan, the regularly used flows are a Q_B of 200 to 250 mL/min and a Q_D of 400 to 500 mL/min. A 2008 survey by the Japanese Society for Dialysis Therapy/Renal Data Registry Committee investigated HD settings and found that the mean Q_B in Japan was 197.4 mL/min and that the mean Q_D was 486.7 mL/min[4]. The flow ratio (Q_B : Q_D) to obtain a well-balanced dialysis efficiency is generally 1 : 2[5,6]. The dialysis efficiency is influenced by the Q_B, Q_D, and the dialyzer's performance, which is expressed as the overall mass transfer area coefficient (K_0A). The equation of clearance (CL) is often used to observe the relation between the dialysis efficiency and the Q_B. The CL represents the amount of blood whose targeted solutes are completely removed per unit time. The CL is the product of solute removal efficiency (the difference between concentration of the inlet and outlet blood, divided by the concentration of the inlet blood) and the Q_B and is expressed as a volume flow rate (mL/min), as are the Q_B and Q_D[1,7]. When all the solutes have been removed from the blood that passes through a dialyzer, the CL and Q_B become equal. Therefore, the CL never exceeds the Q_B[8].

When the Q_D is set at 500 mL/min, which is a regular operating condition *in vitro*, the CL of small-Mw solutes, such as urea (Mw: 60) and creatinine (Cr; Mw: 113), depends strongly on the Q_B, and absolute values of the CL are high[1,7,9]. However, although the CL increases linearly, it reaches a ceiling when the Q_B reaches 200 mL/min[1]. The CLs of large-Mw solutes, such as myoglobin (Mw: 17,000), reach peaks at a Q_B of about 100 mL/min and increase no further[1,9]. The CL's peaking is attributed to the increased Q_B decreasing the time blood stays in the *dialyzer* and decreasing the solute removal efficiency; thus, the CL does not increase in proportion with the Q_B[1]. With large-Mw solutes, the diffusion velocity is lower than with small-Mw solutes; therefore, the CL peaks with a lower Q_B. When the Q_B increases further after the CL peaks, the solute removal efficiency decreases in inverse proportion to the Q_B, and the CL becomes constant[1].

As does the Q_B, the Q_D strongly affects the CL[1,2,7,9]. The relation between the CL and Q_D is similar to that between the CL and Q_B; the CL, like the Q_B, does not exceed the Q_D[1,7]. *In vitro*, as the CL is dependent upon the Q_B, the CL increases in proportion to the Q_D when the Q_B is set at 200 mL/min, which is the regular operating condition; however, the CLs of small-Mw solutes reach a peak with a Q_D of 400 to 500 mL/min[1]. Therefore, the Q_D is usually set at 400 to 500 mL/min, because the Q_B is set at 200 mL/min.

The CL is also influenced by the performance of the dialyzer and its membrane area[2]. When solutes move from the blood side to the dialysis fluid side through semipermeable membranes, the following transfer resistances are present: the membrane resistance (R_M); the blood side film mass-transfer resistance (R_B), which is the resistance of blood flow; and the dialysis fluid side film mass-transfer resistance (R_D), which is the resistance of dialysis fluid flow[10]. The sum of these 3 transfer resistances is the total transfer resistance (R_0). The reciprocal of the R_0 ($1/R_0$) represents how easily the solutes spread by diffusion and is called the overall mass transfer coefficient (K_0)[11]. The K_0 multiplied by membrane area (A) is the K_0A, which is an essential index of a dialyzer's performance and, in common with Q_B, Q_D, and CL, is expressed as a volume flow

rate (mL/min)[12,13].

For small-Mw solutes, the K_0A, Q_B, and Q_D are in the order of $Q_B<Q_D<K_0A$; the CL does not exceed the lowest of these 3 and, so, most strongly depends on the Q_B[13,14]. On the other hand, for large-Mw solutes, the order is $K_0A<Q_B<Q_D$ and, so, the solute removal efficiency most strongly depends on the K_0A, which indicates the membrane's permeability[13]. The Q_D influences the solute removal efficiency of small-Mw and large-Mw solutes secondarily or thirdly[2,13]. These facts indicate that the Q_B, Q_D, and K_0A are closely related to the solute removal efficiency during HD and that the CL depends on the balance of these 3 parameters. In particular, to make the best use of a high-performance dialyzer with a high K_0A, both the Q_B and Q_D must be increased to maintain the flow ratio (Q_B : Q_D) at 1 : 2 or greater[5]. Recently, because the R_M has decreased as membrane performance has improved, the R_B and R_D account for a greater share of the total resistance[13].

In conventional HD, most medium-Mw and large-Mw solutes are removed through ultrafiltration; whereas, in recent high-performance dialyzers, even medium-Mw and large-Mw solutes are dependent on the Q_B and Q_D[3,8,14]. Small-Mw proteins, such as β_2 microglobulin (β_2-MG; Mw: 11,800), can be removed through diffusion as well as through ultrafiltration; therefore, the solute removal efficiency improves as the Q_B increases. Thus, the HD settings are becoming even more important. Considering the flow ratio, a Q_D of 500 mL/min seems to be slightly insufficient for dialyzers with large, high-performance membranes with a Q_B of 300 mL/min or higher to actively remove medium-Mw and large-Mw solutes. Conversely, a Q_D of 500 mL/min seems to be excessive when the Q_B is set at 100 to 120 mL/min for the introductory stage of dialysis.

In Japan, the expenses for dialysis fluid are included in the procedure fee, and recently, environmental pollution by waste dialysis fluid has been considered a problem; therefore, it is essential to consider the financial and environmental aspects of HD. Well-balanced operating conditions are financially and environmentally conscious and can even become useful countermeasures against water being in short supply, as in times of disaster.

In the present study, we performed HD with the Q_D reduced from 500 mL/min to 400 mL/min and investigated the effects of this reduction on dialysis efficiency. Furthermore, in cases in which the dialysis efficiency decreased due to the reduced Q_D, we calculated a new Q_B with the K_0A equation so that the CL would be equivalent to that before the reduction of the Q_D; we then evaluated whether the equivalent dialysis efficiency could be secured with a Q_D of 400 mL/min and the calculated Q_B.

Materials and Methods

The subjects were 12 patients undergoing chronic dialysis in 2 of our corporate member facilities. Of these subjects, 9 were men and 3 were women; their mean age was 69.0 ± 10.1 (mean ± standard deviation) years; the average duration of dialysis was 5.5 ± 1.2 (mean ± standard deviation) years; and the primary diseases were diabetic nephropathy (n=7), chronic glomerulonephritis (n=4), and unknown (n=1). These patients were assigned to undergo HD with 1 of the following 2 conditions: 1) HD with 1.3-m^2 polysulfone membranes for 4 hours under the moderate settings of a Q_B of 150 mL/min and a Q_D of 500 mL/min (n=6); and 2) HD with 1.6-m^2 polysulfone membranes for 4 hours with the standard settings of a Q_B of 200 mL/min and a Q_D of 500 mL/min (n=6). To be included, patients should have stable hemodynamics without marked anemia.

We used 2 types of polysulfone-membrane dialyzers with different membrane areas: the TS-1.3 U (Toray Medical Co., Ltd., Chiba) and the TS-1.6UL (Toray Medical Co., Ltd.,) with membrane areas of 1.3 m^2 and 1.6 m^2, respectively. For the TS-1.3U dialyzer, the settings were a Q_B of 150 mL/min and a Q_D of 500 mL/min; for the TS-1.6UL dialyzer, the settings were a Q_B of 200 mL/min and a Q_D of 500 mL/min. The setting that was each patient's regular dialysis setting was designated "condition A," and the setting with the Q_D decreased by 100 mL/min (to 400 mL/min) was designated "condition B" (**Fig. 1**).

In a crossover trial, each patient underwent HD under conditions A and B for 2 weeks each. We evaluated the following variables for the removal of small-Mw and large-Mw solutes: CL, the reduction

n=6

Dialyzer	Condition A	Condition B
Toray TS-1.3U (1.3 m²)	Q_B=150 mL/min Q_D=500 mL/min	Q_B=150 mL/min **Q_D=400 mL/min**
Toray TS-1.6UL (1.6 m²)	Q_B=200 mL/min Q_D=500 mL/min	Q_B=200 mL/min **Q_D=400 mL/min**

Fig. 1 Conditions of HD in the primary study
Six patients were selected to undergo HD with a TS-1.3U dialyzer and with a TS-1.6UL dialyzer. Condition A was defined as the regular operating condition, and condition B was defined as the condition in which the Q_D was decreased by 100 mL/min from that in condition A. Both conditions were performed for 2 weeks in a crossover trial, and the removal of various solutes was evaluated.
Q_B: blood flow rate, Q_D: dialysis fluid flow rate

n=6

Dialyzer	Condition A	Condition B'
Toray TS-1.6UL (1.6 m²)	Q_B=200 mL/min Q_D=500 mL/min	**Q_B=210 mL/min** **Q_D=400 mL/min**

$$KoA\,(mL/min) = \frac{Q_B}{1 - Q_B/Q_D} \ln\left(\frac{1 - CL/Q_D}{1 - CL/Q_B}\right)$$

Fig. 2 Conditions of HD in the re-evaluation
Condition B' was defined as the operating condition with the obtained Q_B and the Q_D decreased by 100 mL/min and was compared with condition A.

rate (RR), removal amount (RA), clear space (CS), and the CS rate (**Fig. 6**); we also evaluated albumin (Mw: 66,000) leakage. The values of these variables are expressed as means ± standard deviations. Significance was tested with paired *t*-tests, and a p value of <5% was considered to indicate statistical significance. To evaluate the removal of small-Mw solutes, we used urea nitrogen (UN; Mw: 28), creatinine (Cr; Mw: 113), uric acid (UA; Mw: 168), and inorganic phosphorous (iP; Mw: 30). For large-Mw solutes, we used β_2 microglobulin (β_2-MG Mw: 11,800) and α_1 microglobulin (α_1-MG; Mw: 33,000). To determine the CS rate, we used UN and β_2-MG exclusively.

If the dialysis efficiency of condition B was significantly lower than that of condition A for the evaluation of solute removal, we performed a supplementary test. We calculated the Q_B to achieve a dialysis efficiency equivalent to that of condition A using the K_oA equation; condition B' was defined as that with the calculated Q_B and a Q_D of 400 mL/min; and the removal of each solute was re-evaluated to investigate whether the dialysis efficiency of condition B' was equivalent to that of condition A (**Fig. 2**). In addition, we monitored the transition of the blood pressure during dialysis under each operating condition to investigate the effect on hemodynamics of the increase in Q_B. Furthermore, blood samples for evaluating solute removal were obtained at the same time as the patients' periodic blood tests to avoid excessive blood draws while we performed evaluations in the 2 facilities. The volume of blood samples for each evaluation was 10 mL (4 mL from the arterial circuit and 4 mL from the venous circuit for biochemical analysis, and 2 mL from the arterial circuit for blood counts), which was required to measure CL 60 minutes after the start of dialysis. The volume of blood samples for the

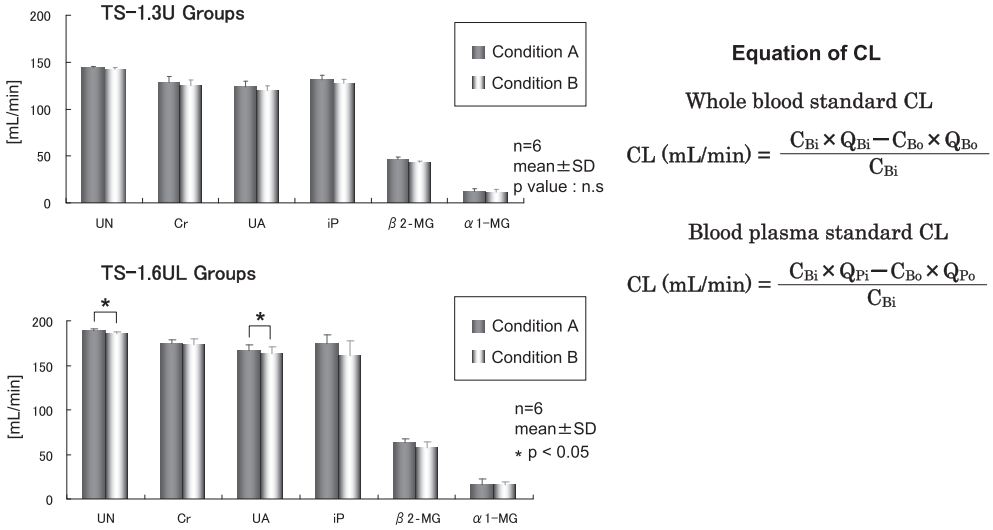


Fig. 3 Results of clearance in the primary study

To determine CL, blood was collected from the venous circuit (the outlet of dialyzers) and, then, from the arterial circuit (the inlet of dialyzers) 60 minutes after the start of dialysis, and the solute concentrations were calculated at the inlet and outlet of the dialyzers. Furthermore, water removal is involved in most cases of the regular HD, so the Q_B is decreased by amount of the water removal. Therefore, the Q_B differs at the inlet and the outlet, and we used the equation that is corrected by water removal. The filtration rate (Q_F) was uniformly set at 10 mL/min/m^2 at the time of sampling, and blood was collected 5 minutes later. Moreover, for small-Mw solutes, we used the whole-blood standard CL, which is substituted by total blood flow, because small-Mw solutes can be transported into and out of blood cells; for large-Mw solutes, we used the plasma standard CL, in which the plasma flow rate (Q_P) is calculated from the hematocrit and is substituted for the Q_B, because large-Mw solutes are slowly transported into and out of blood cells, and during the time blood is in the dialyzers, their transportation from inside of blood cells was extremely slight.

UN: urea nitrogen; Cr: creatinine; UA: uric acid; iP: inorganic phosphorus; β_2-MG: β_2 microglobulin; α_1-MG: α_1 microglobulin; Q_{Bi}: inlet blood flow rate; Q_{Bo}: outlet blood flow rate; C_{Bi}: concentration of inlet blood; C_{Bo}: concentration of outlet blood; Q_{Pi}: plasma flow rate of inlet blood; Q_{Po}: plasma flow rate of outlet blood

crossover trial was 20 mL; even if the re-evaluation was performed, the total volume of blood samples would be 30 mL for a 6-week period. In this evaluation, the condition with the reduced Q_D was manipulated within the range of a Q_B : Q_D flow ratio of 1 : 2 or greater, which is considered a necessary condition for balanced dialysis efficiency. The evaluation period was short: a maximum of 4 weeks with the reduced Q_D, and a maximum of 6 weeks when re-evaluation was included. Moreover, we selected patients who did not have severe anemia and whose hemodynamic conditions were stable during dialysis. The aims of the study were explained to all subjects, and informed consent was obtained. With these safeguards, we assumed that the study protocol did not violate the ethics policies of our institutions.

Results

The results of solute removal performance under the crossover trial of conditions A and B were as follows. With the TS-1.3U dialyzer, the differences in CL between conditions A and B for both small-Mw and large-Mw solutes were slight and were not significant. Similarly, with the TS-1.6UL dialyzer, the differences in CL between conditions A and B were slight, but the CLs of both UN (188.3 ± 2.7 mL/min) and UA (166.6 ± 6.8 mL/min) in condition A were significantly higher than those in condition B (UN: 185.5 ± 2.3 mL/min, p=0.0243; UA: 163.2 ± 7.4 mL/min, p=0.0092, **Fig. 3**).

The RRs with the TS-1.3U dialyzer for iP, a small-Mw solute, in conditions A and B were 50.9% ± 6.5%

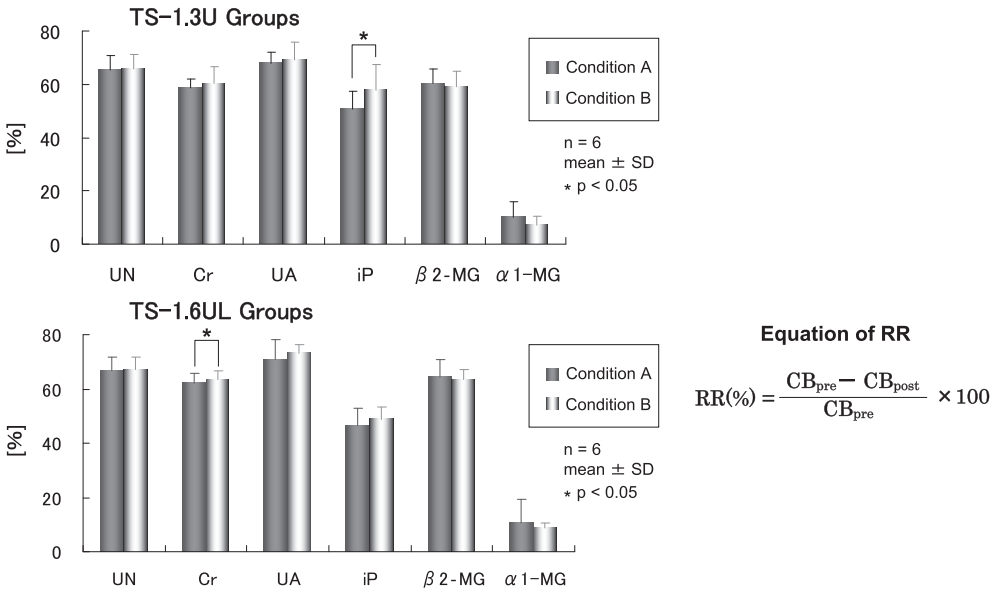


Fig. 4 Results of reduction rate in the primary study

The RR is derived from the predialysis and postdialysis blood-side solute concentrations. For large-Mw solutes, whose transportation velocity is low, we corrected the postdialysis solute concentration with predialysis and postdialysis hematocrit values, because they are affected by water removal.

C_{Bpre}: solute concentration at the beginning of dialysis, C_{Bpost}: solute concentration at the end of dialysis (For other abbreviations, see Fig. 3)

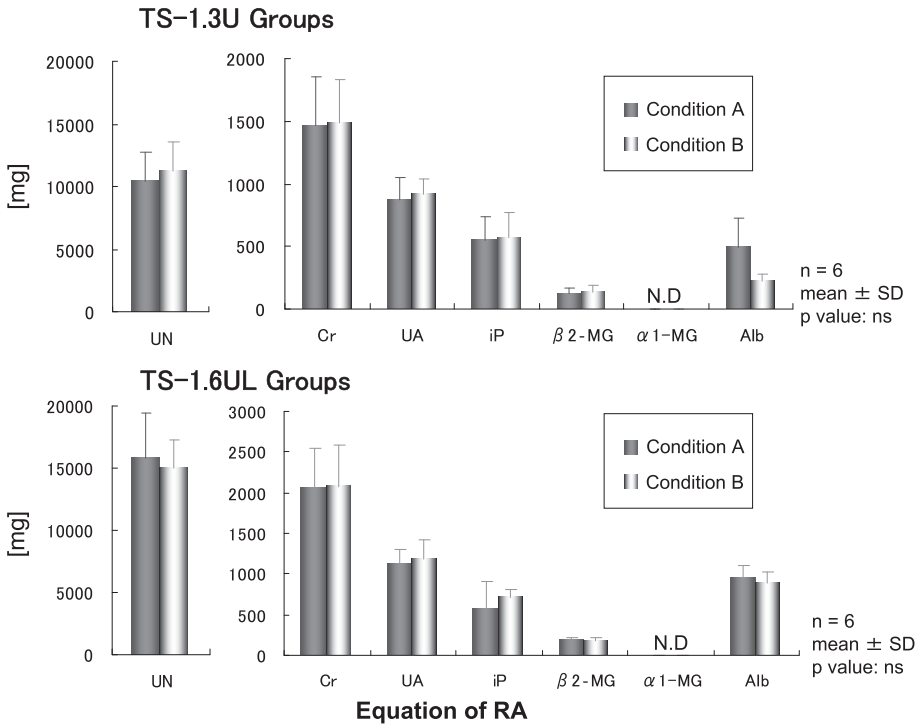
and 58.0% ± 9.4% (p=0.0267), respectively. With the TS-1.6UL dialyzer, the RRs for Cr in conditions A and B were 61.9% ± 3.8% and 63.7% ± 3.1% (p= 0.0215), respectively. Contrary to our expectations, these values were higher in condition B than in condition A. For other solutes, the differences between the dialyzers were slight and were not statistically significant **(Fig. 4)**. In addition, the RA, albumin leakage, CS, and the CS rate did not differ between condition A and condition B **(Fig. 5, 6)**. Because the CLs of UN and UA were significantly lower in condition B than in condition A with the TS-1.6UL dialyzer, we calculated the Q_B with the K_0A equation for a Q_D of 400 mL/min to make the CL equivalent to that of condition A. The calculated Q_B was 205 mL/min for UA and 209 mL/min for UN. Thus, we set condition B' as a Q_B of 210 mL/min and a Q_D of 400 mL/min, re-examined the removal performance for each solute, and compared the results with those of condition A.

The CL of UA in condition B' (165.9 ± 10.9 mL/min) did not differ significantly from that in condition A (166.6 ± 6.8 mL/min, p=0.8407), but the CL of UN in condition B' (192.2 ± 3.1 mL/min) was significantly higher than that in condition A (188.3 ± 2.7 mL/min, p=0.0046, **Fig. 7a**).

The RR of Cr in condition A (61.9% ± 3.8%) did not differ significantly from that in B' (63.3% ± 3.8%, p=0.1493). However, the RR for iP was significantly higher in condition B' (55.0% ± 4.3%) than in condition A (46.3% ± 6.4%, p=0.0467, **Fig. 7b**). The RA, the CS, and the CS rate did not differ significantly between condition A and condition B', but albumin leakage in condition B' was significantly lower than that in condition A **(Fig. 8)**. Furthermore, the blood pressure during HD was stable in all conditions, and the increased Q_B in condition B' had no effect on hemodynamics **(Fig. 9)**.

Discussion

In HD, the Q_D is generally set at 500 mL/min because Babb et al. showed that the theoretical maximum solute removal efficiency of Kiil-type dialyzers is achieved when the Q_D is 3 times the Q_B[15]. We now use hollow-fiber dialyzers, so this setting might not be appropriate. However, when the Q_B is set at 200 mL/min, which is the mean value in



Equation of RA

**RA (mg) = solute concentration in waste dialysis fluid ×
(total dialysis fluid amount + total water removal)**

Fig. 5 The results of removal amount in the primary study

The RA was calculated by multiplying the waste fluid volume by the solute concentration of the waste dialysis fluid. There are 2 methods of pooling the waste dialysis fluid: 1) to collect all the waste fluid and 2) to collect part of the waste fluid continuously. The former method requires complicated procedures because approximately 120 L of fluid (dialysis fluid flow of 500 mL/min × 240 min) is collected per dialysis session. Thus, we used the latter method, which is easier to perform. For this evaluation, we pooled a volume of waste fluid corresponding to the ultrafiltration from the outlet of a drainage pump. We calculated the RA by multiplying the solute concentration of this volume of waste fluid and the total waste dialysis fluid volume (the sum of the total ultrafiltration volume and the total dialysis fluid amount) per dialysis session.

Alb: albumin (For other abbreviations, see Fig. 3)

Japan, the CLs of small-Mw solutes show strong Q_D-dependence until the Q_D reaches 400 to 500 mL/min[1]. Thus, a Q_D of 500 mL/min seems to be appropriate, even for hollow-fiber dialyzers, if the Q_B is around 200 mL/min. The CLs of small-Mw substances are strongly affected by both the Q_B and Q_D, and to achieve a balanced dialysis efficiency, it is important to increase both the Q_B and Q_D. The flow ratio (Q_B : Q_D) to achieve a balanced dialysis efficiency is generally said to be 1 : 2[5]. However, because modifying the Q_D of conventional dialyzers for each patient, as the Q_B has been, is difficult, the Q_D is uniformly set at 500 mL/min to match a Q_B of 200 to 250 mL/min, which is typical for maintenance dialysis in Japan. Nevertheless, a Q_D of 500 mL/min seems to be excessive when the Q_B is set as low as 100 to 150 mL/min for patients who are in the introductory stage of maintenance dialysis or are elderly or in whom the cardiovascular effects must be carefully monitored. On the other hand, in the United States and Europe, the Q_B is maintained as high as 400 to 500 mL/min; so, in such conditions, the dialysis efficiency can be improved if the Q_D is increased to greater than 500 mL/min[2]. Recently, new types of dialyzer allow the Q_D to be modified for each patient, so that setting well-balanced operating conditions is now possible for each patient.

In the present study, we decreased the Q_D by 100

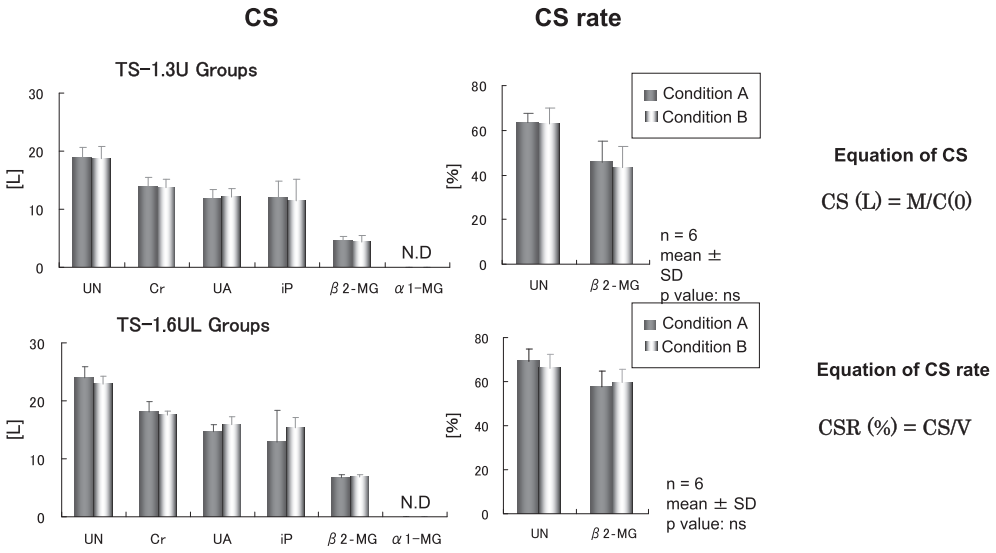


Fig. 6 Results of CS and the CS rate in the primary study

We calculated the CS by dividing the targeted RA by the predialysis blood-side solute concentration. The RR and the RA are affected by the predialysis solute concentration; a higher predialysis solute concentration is associated with a higher RR and RA; in contrast, the CS is corrected by the predialysis solute concentration and is less easily affected. The CS rate is the standardized value calculated by dividing the CS by the solute biodistribution volume (V) of the patients' targeted solutes and is useful for comparing patients. The V of UN was calculated as 60% of the dry weight of the patients, and the V of β_2-MG was calculated as 20% of the dry weight.

M: RA; C (0): solute concentration at the beginning of dialysis (For other abbreviations, see Fig. 3.)

mL/min from 500 mL/min to 400 mL/min to investigate the effect on dialysis efficiency of a Q_B of 200 mL/min (the general setting for maintenance dialysis) and a Q_B of 150 mL/min (a more moderate setting) in polysulfone-membrane dialyzers, which are the most widely used dialyzers in Japan. We used membranes with areas of 1.3 m^2 and 1.6 m^2 **(Fig. 1)**. In a crossover trial, we assigned patients to both conditions A and B and evaluated the RRs of various solutes. With the TS-1.3U dialyzer, the CLs of conditions A and B were similar, and the differences were not significant. In contrast, with the TS-1.6UL dialyzer, the CLs of the small-Mw solutes UN and UA were significantly lower in condition B **(Fig. 3)**. The Q_B with the TS-1.3U dialyzer was 150 mL/min, and the flow ratio (Q_B : Q_D) was maintained at higher than 1 : 2, even in condition B, in which the Q_D was 400 mL/min, 100 mL/min lower than that in condition A; thus, the reduction in Q_D had little effect on solute removal. The Q_B of the TS-1.6 UL dialyzer was 200 mL/min, and the flow ratio (Q_B : Q_D) was 1 : 2 when the Q_D was reduced to 400 mL/min. This operating condition is required to maintain the minimum flow ratio for balanced dialysis efficiency; therefore, the reduced Q_D might have affected solute removal to some extent. In light of these facts, the flow ratio (Q_B : Q_D) should be at least 1 : 2 and should, ideally, be greater. Both the RR for iP with the TS-1.3U dialyzer and the RR for Cr with the TS-1.6UL dialyzer were significantly higher in condition B than in condition A **(Fig. 4)**; these results were contrary to our expectations. The RR is easily affected by the predialysis values of solutes; a higher predialysis value is associated with a higher RR[16]. The present study was a crossover trial, and the values of small-Mw solutes before the start of dialysis were generally higher in condition B than in condition A; therefore, these predialysis values might have affected the RRs. In particular, the predialysis value of iP with the TS-1.3U dialyzer was higher in condition B (5.4 ± 1.3 mg/dL) than in condition A (4.5 ± 0.7 mg/dL), although the difference was not significant (**Table 1**). The RA is also dependent on predialysis values[17]. As with the

Figure 7a. Results of CL in the re-evaluation

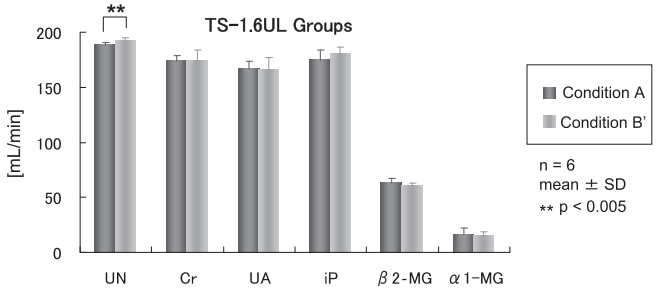


Figure 7b. Results of reduction rate in the re-evaluation

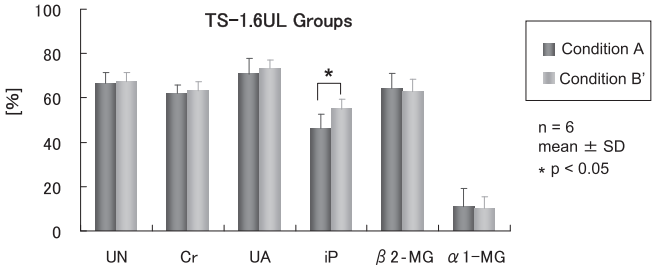


Fig. 7 Results of CS and the CS rate in the re-evaluation
With the TS-1.6UL dialyzer, we re-evaluated the clearance and reduction rate and compared them in condition A and B.
For abbreviations, see Fig. 3.

RRs, the RAs of small-Mw solutes were slightly higher in condition B; however, because the RAs varied widely, the differences were not significant **(Fig. 5)**. Even when the predialysis values were controlled, there was no significant difference in the CS or the CS rate **(Fig. 6)**.

As mentioned above, we evaluated the removal of various solutes in condition A (Q_D=500 mL/min) and condition B (Q_D=400 mL/min) and obtained similar results with the 2 conditions. However, because, with the TS-1.6UL dialyzer, the CLs of the small-Mw solutes UN and UA were significantly lower in condition B **(Fig. 3)**, we used the K_0A equation to calculate a Q_B for a Q_D of 400 mL/min to make the CL equivalent to that in condition A. The Q_B calculated for a Q_D of 400 mL/min was 210 mL/min, and we defined this condition as condition B' and re-evaluated solute removal with this condition and with condition A **(Fig. 2)**. We found no significant difference in the CL of UA between condition A and condition B'; on the other hand, the CL of UN was significantly higher in condition B' **(Fig. 7a)**, which showed a correlation with the theoretical values of K_0A. Also, when the Q_D is reduced by 20%, an increase of the Q_B by only about 5% allows the CL to be greater or equal to that of condition A. Thus, as in *in vitro* evaluations, we confirmed in the present study that the CL of small-Mw solutes is strongly dependent on the Q_B. The re-evaluation comparison between conditions A and B' showed no significant difference in the RR of Cr **(Fig. 7b)**, which showed a significant difference preevaluation owing to its dependence on predialysis values **(Fig. 4)**. In addition, we found no significant difference in the RR of iP between conditions A and B, but the RR in condition B' was significantly higher than that in condition A. However, the RRs of other small-Mw solutes did not differ significantly between conditions A and B'. Furthermore, although the predialysis value of iP was 4.2 ± 0.9 mg/dL in condition A, it was significantly higher (5.0 ± 0.7 mg/dL) in condition B'. In light of these findings, the significantly higher RR of iP in condition B' appears to be due to the predialysis value, rather than to the increased Q_B. Albumin leakage in condition B' was significantly less than that in condition A. We considered it a good result in terms of improving nutritional status.

We have confirmed that, by increasing the Q_B to the value calculated with the K_0A equation, dialysis

Figure 8a. Results of RA in the re-evaluation

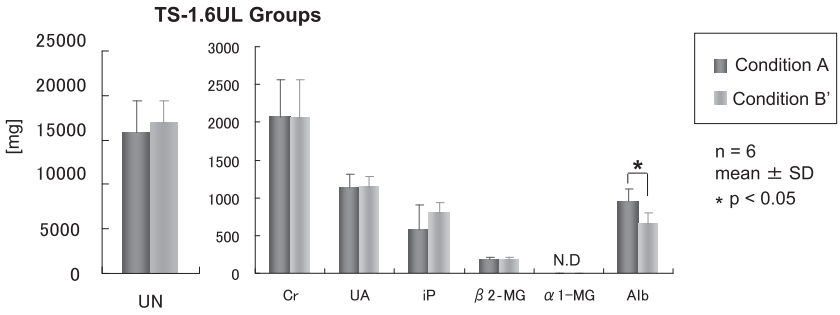


Figure 8b. Results of CS and CS rate in the re-evaluation

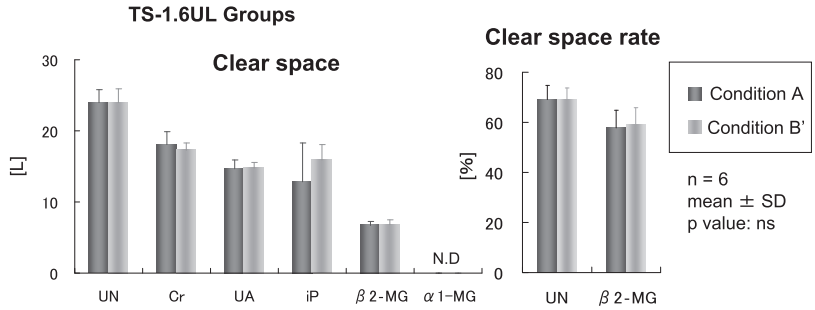


Fig. 8 Results of RA, CS, and CS rate in the re-evaluation
With the TS-1.6UL dialyzer, we re-evaluated the RA, CS, and CS rate and compared them between conditions A and B.

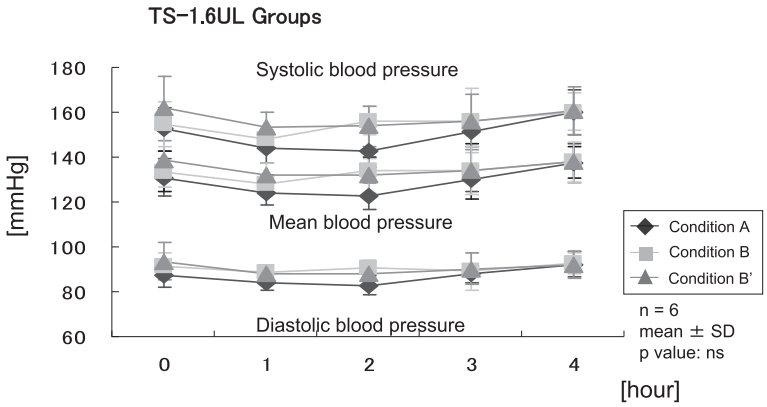


Fig. 9 Fluctuation of systolic blood pressure under each operating condition
With the TS-1.6UL dialyzer, we recorded the blood pressures every hour during HD to investigate how conditions A, B, and B' affect hemodynamics.

efficiency can be maintained despite a decrease in the Q_D. This method is extremely useful for maintaining dialysis efficiency when the Q_D needs to be uniformly reduced for a long time, such as when dialysis fluid is in short supply during natural disasters; however, in regular clinical practice, the Q_B should not be increased simply to reduce the Q_D. The Q_B and a well-balanced dialysis efficiency, achieved through a combination of the Q_B, Q_D, and K_0A, should be the priorities; therefore, the Q_D should be adjusted for the Q_B. Moreover, this study confirmed the possibility of decreasing the Q_D when the flow ratio (Q_B : Q_D) is maintained at 1 : 2 or greater under moderate operating conditions with a Q_B of around 150 mL/min. On the other hand, when a high Q_B of 300 mL/min and high-performance, large-area

Table 1 Predialysis values

TS-1.3U Groups		UN	Cr	UA	iP	β2-MG	α1-MG
Condition A	pre-HD (mg/dL)	55.5 ± 12.9	10.5 ± 2.1	7.4 ± 0.9	4.5 ± 0.7	28.9 ± 7.7	125.3 ± 28.0
Condition B	pre-HD (mg/dL)	60.8 ± 11.4	10.7 ± 2.2	8.8 ± 2.3	5.4 ± 1.3	33.4 ± 13.8	126.7 ± 24.3
Condition A vs. Condition B		n.s	n.s	n.s	n.s	n.s	n.s

TS-1.6UL Groups		UN	Cr	UA	iP	β2-MG	α1-MG
Condition A	pre-HD (mg/dL)	66.7 ± 17.5	11.5 ± 2.8	7.8 ± 1.5	4.2 ± 0.9	27.2 ± 3.5	119.1 ± 14.2
Condition B	pre-HD (mg/dL)	66.5 ± 13.0	11.7 ± 2.8	7.5 ± 1.0	4.7 ± 0.9	26.1 ± 3.4	115.6 ± 17.3
Condition B'	pre-HD (mg/dL)	71.5 ± 12.4	11.8 ± 2.6	7.7 ± 1.2	5.0 ± 0.7	26.3 ± 2.5	114.6 ± 11.3
Condition A vs. Condition B		n.s	n.s	n.s	$p < 0.05$	n.s	n.s
Condition A vs. Condition B'		n.s	n.s	n.s	$p < 0.01$	n.s	n.s

n = 6
Mean ± SD
Paired *t*-test

membrane dialyzers are used to achieve a high dialysis efficiency, we assume that it would be more effective to increase Q_D to greater than 500 mL/min to match the higher Q_B. We also observed changes in the blood pressure with each operating condition during HD, but the changes did not differ significantly among the conditions. Even in condition B', an expected effect of the increased Q_B on hemodynamics was not observed, probably because the increase in the Q_B was only 10 mL/min.

For further investigations, we are considering a long-term evaluation of additional variables, such as the time-averaged concentration and the weekly average CL. In the present study, we used dialyzers made by the same manufacturer and with the same type of membrane with areas of 1.3 m^2 (small) and 1.6 m^2 (regular size). However, we believe future evaluations should involve larger membranes or different types of membrane to examine the effects on internal-filtration-enhanced HD. In dialyzers that have high-performance membranes with larger pores, a pressure gradient develops owing to the countercurrent operation of blood and dialysis fluid. Because of this pressure gradient, filtration occurs from the blood to the dialysis fluid around the blood inlet, and back-filtration occurs from the dialysis fluid to the blood around the blood outlet. Engineering advances, such as longer dialyzers and increased hollow-fiber density, increase the pressure loss, and this phenomenon is exploited by internal-filtration-enhanced dialyzers. With such dialyzers, the ability to remove medium- and large-Mw solutes is as good as with hemodiafiltration. The pressure gradient occurs due to the variation in the Q_D and might affect the amount of internal filtration. Thus, it is extremely important to determine whether the expected amount of internal filtration can be obtained and whether the solute removal performance of medium- and large-Mw solutes can be maintained. Therefore, comprehensive evaluation to guarantee the well-balanced dialysis efficiency is warranted for clinical application.

Conclusion

In HD, the Q_B : Q_D ratio must be maintained at 1 : 2 or greater for balanced dialysis efficiency, and the Q_D can be reduced as long as this ratio is maintained. Setting a highly efficient Q_D can be financially and environmentally conscious. In addition, use of the K_0A equation is a highly effective method for calculating a Q_B that allows an expected dialysis efficiency to be achieved despite a need to reduce the Q_D when dialysis fluid is in short supply, as in times of disaster.

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