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An Index of Plasma Refilling in Hemodialysis Patients

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Key Words
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Abstract

During hemodialysis therapy, a large amount of water is removed from the patient's blood in a short time; however, blood pressure remains stable in most patients. As water is removed, the circulating serum proteins become more concentrated, resulting in a marked increase in the driving force which pulls water from the extravascular space into the blood vessels, by a process called plasma refilling. However, since a method for studying plasma refilling has not previously been proposed, it is not known what determines the plasma refilling capacity of hemodialysis patients. To evaluate the plasma refilling capacity of patients, we propose here a method for calculating an index of plasma refilling capacity, which we have called the plasma-refilling coefficient (Kr).

In 14 patients receiving maintenance hemodialysis therapy, total serum protein was measured before hemodialysis, and hematocrits were measured hourly during hemodialysis. From the changes in the hematocrits, we estimated the changes in the circulating plasma volume and in the intracapillary oncotic pressure at each time point. The water removal rate was also measured hourly. From these values, we calculated Kr. An averaged volume of 2,692 ± 219 ml of water was removed from each patient resulting in a decrease in the estimated circulating blood volume, while the hematocrit and the estimated intracapillary oncotic pressure increased gradually. Kr calculated after 1 h of hemodialysis varied widely between patients, 140.3–1,744.2 ml/mm Hg/h, and decreased gradually as water removal continued. The average Kr of 14 patients was 698.9 ± 15.2 ml/mm Hg/h at the beginning of water removal, and it decreased to 405.3 ± 75.4, 203.9 ± 39.5, 130.2 ± 20.5 and 93.9 ± 14.3 each hour thereafter.

The index of plasma refilling proposed in this paper is useful for examining capillary water permeability and the degree of plasma refilling in hemodialysis patients.

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Introduction

Hemodialysis therapy is applied in cases of chronic renal failure to remove uremic substances and to correct electrolyte and fluid imbalances. In some patients the increase in body weight over the interdialysis period exceeds 5% of their body weight. A large volume of excess water is rapidly removed during 4 or 5 h of hemodialysis, which frequently results in the development of hypotension [1]. However, the incidence and magnitude of hypotension varies from patient to patient, even when the water removal rate is the same. Although the variation in the patients' plasma-refilling rates would probably account for the variation in hypotension development, a method for clinically evaluating the plasma-refilling capacity of patients has not previously been proposed.

A subject's plasma volume and interstitial fluid volume can be measured using [^{125}I]albumin or [^{51}Cr]EDTA [1, 2]. Clinically, however, these methods are inconvenient and hazardous. Schneditz et al. [3] studied plasma volume during ultrafiltration using the estimated intracapillary oncotic pressure, which they calculated from the plasma density. However, they only examined the changes in plasma volume over a short period, as they assumed that the ultrafiltration coefficient remained almost constant during ultrafiltration.

In this paper, we present a mathematical model for calculating the plasma-refilling coefficient. This index is useful for evaluating the plasma-refilling capacity of patients and the effects of the vasoactive substances on capillary water permeability during hemodialysis therapy.

Abbreviations

C_P	total serum protein concentration [g/dl]
Ht	hematocrit [%]
J_V	volume flow across a membrane [ml/min]
Kr	plasma refilling coefficient [ml/mm Hg/h]
P_A	hydrostatic pressure in capillary at arterial side [mm Hg]
Pc	mean hydrostatic pressure in capillary [mm Hg]
Pi	interstitial hydrostatic pressure [mm Hg]
πi	interstitial oncotic pressure [mm Hg]
πp	intracapillary oncotic pressure [mm Hg]
P_V	intracapillary hydrostatic pressure at the venous end [mm Hg]
R_A	capillary resistance at the arterial end
R_V	capillary resistance at the venous end
R_V/R_A	capillary resistance ratio between the arterial and venous ends
σ	capillary water permeability [ml/mm Hg/min]
TP	total amount of serum protein [g]
Uf	ultrafiltration rate [ml/h]
VB	red blood cell mass [l]
V_P	circulating plasma volume [ml]
W_b	body weight before hemodialysis [kg]

Patients and Methods

For 14 patients undergoing chronic maintenance hemodialsis (8 men and 6 women; average age 53.4 ± 3.8 years, range 22–72; average duration of hemodialysis therapy was 32.8 ± 11.0 months, range 1–135), the plasma refilling coefficient, Kr, was evaluated during a single session of hemodialysis. Profiles of the patients are listed in table 1.

To calculate Kr, the serum protein concentration (g/dl) was measured before hemodialysis, and hematocrits (Ht, %) were measured before hemodialysis, just before the start of water removal, and every hour during hemodialysis. The priming volume of the dialyzer and its circuit was about 200 ml, and just after connection of the patient to the circuit, the circulating blood was diluted with priming saline. Water removal started about 15 min after connection and volume of water removed was monitored using personal consoles (model DBB-22B; Nikkiso, Tokyo, Japan). During hemodialysis, the water removal rate was kept constant, as listed in table 1.

Parameters Used in the Calculation of Kr (Plasma-Refilling Coefficient)

In general, water transport across the capillary wall is expressed by Starling's law [4],

$$J_V = \sigma[(\pi p - \pi i) - (Pc - Pi)]$$

where J_V is the volume flow across the membrane, σ is the capillary water permeability, πp is the intracapillary oncotic prssure, πi is the interstitial oncotic pressure, Pc is the intracapillary hydrostatic pressure, and Pi is the interstitial hydrostatic pressure. In hemodialysis patients, the circulating plasma volume during hemodialysis is determined by both the water removal rate (Uf, ultrafiltration rate) and the rate of plasma refilling by fluid movement from the interstitial space into the capillaries. Thus the change in the circulating plasma volume, V_P, is expressed by

$$dV_P/dt = Kr[(\pi p(t) - \pi i) - (Pc - Pi)] - Uf \quad (1)$$

where dV_P/dt is the time-dependent change in the circulating plasma volume, Kr is the plasma-refilling coefficient and $\pi p(t)$ is the intracapillary plasma oncotic pressure at a time t.

To calculate Kr, the individual parameters in equation 1 were determined as follows:

V_P: the circulating plasma volume: The circulating blood volume is estimated to be about 7.7% of the body weight, so the circulating plasma volume before hemodialysis is

$$V_{Pb} = 0.077\ W_b(1 - Ht_b/100) \quad (2)$$

where W_b is the body weight before hemodialysis, and Ht_b is the hematocrit before hemodialysis.

πp: the oncotic pressure: πp is calculated by the following equation [5],

$$\pi p = 2.1\ Cp + 0.16\ Cp^2 + 0.012\ Cp^3 \quad (3)$$

where Cp is the total serum protein [g/dl].

Table 1. Patient profiles

Case	Age years	Sex	HD duration months	Etiology	BW kg	TP g/dl	Water removal rate, ml/h	Water removal volume, ml	Ht %
M.K.	42	F	1	CGN	44.6	5.6	470	1,880	15.8
S.D.	67	M	1	CGN	53.8	6.0	900	3,600	24.9
O.H.	47	M	2	CGN	51.2	4.8	350	1,400	22.1
K.H.	22	F	3	CGN	53.3	5.8	560	2,000	26.6
K.S.	68	M	3	CGN	66.5	6.0	630	2,200	20.5
N.T.	72	M	10	CGN	54.9	6.4	770	2,600	29.7
S.S.	56	M	19	CGN	45.4	6.6	600	2,400	22.5
S.Y.	65	F	27	CGN	44.7	5.8	690	2,500	26.4
A.K.	48	F	28	CGN	51.6	5.8	840	3,360	20.1
N.K.	44	F	28	CGN	50.3	5.3	1,050	4,200	19.4
K.K.	40	F	30	CGN	33.8	6.0	900	3,600	20.0
H.T.	65	M	72	NS	60.7	5.7	550	1,900	31.8
S.H.	62	M	100	CGN	73.0	8.6	940	3,410	23.1
S.O.	50	M	135	CGN	56.1	5.0	660	2,640	22.9
Mean	53.4		32.8		52.9	6.0	707.9	2,692.1	23.3
SE	3.8		11.0		2.6	0.2	53.3	218.6	1.1

CGN = Chronic glomerulonephritis; NS = nephrosclerosis.

Pc, Pi, πi: mean hydrostatic pressure, interstitial hydrostatic pressure, and interstitial oncotic pressure: If the net water movement between the capillaries and the interstitium was in a state of equilibrium before the start of water removal in hemodialysis, we could assume that the driving force in equation 1 was nominally zero between the two compartments. In this case the value of the intracapillary oncotic pressure before water removal (πp(0)) would satisfy by the equation

$$Kr[(\pi p(0) - \pi i) - (Pc - Pi)] = 0$$

therefore

$$(\pi p(0) - \pi i) - (Pc - Pi) = 0$$

and πp(0) is therefore given by

$$\pi p(0) = \pi i + Pc - Pi \quad (4)$$

Assuming that the changes in πi, Pc, and Pi during water removal are much smaller than the change in πp(t), the change in the driving force during hemodialysis can be estimated by combining equations 1 and 4:

$$(\pi p(t) - \pi i) - (Pc - Pi) = \pi p(t) - (\pi i + Pc - Pi) = \pi p(t) - \pi p(0) \quad (5)$$

$V_P(t)$: changes in the circulating plasma volume: Change in the circulating plasma volume during hemodialysis can be calculated from the changes in the hematocrit. As the red blood cell mass (VB) does not change during water removal, VB is calculated from

$$Ht_b/100 = VB/(Vpb + VB), \text{ and}$$

$$Ht(t)/100 = VB/(V_P(t) + VB)$$

which can be rearranged as

$$V_{Pb}/VB + 1 = 100/Ht_b, \text{ and}$$

$$V_P(t)/VB + 1 = 100/Ht(t)$$

giving

$$VB = V_{Pb}/(100/Ht_b - 1), \text{ and}$$

$$VB = V_P(t)/(100/Ht(t) - 1)$$

Thus the circulating plasma volume at a time (t), $V_P(t)$ is

$$V_P(t) = V_{Pb}(100/Ht(t) - 1)/(100/Ht_b - 1)$$

$$= 0.077\ BW(Ht_b/100)(100/Ht(t) - 1) \quad (6)$$

where V_{Pb} and $V_P(t)$ denote the circulating plasma volume before the start of water removal, and at a time (t). Ht_b and Ht(t) denote the hematocrit before the start of water removal, and at a time (t).

$C_P(t)$: total serum protein concentration at time (t): $C_P(t)$ during hemodialysis was calculated from the hematocrit measurements. As the total amount of serum protein (TP) in the circulation does not change during hemodialysis,

$$C_{Pb} = TP/Vpb \quad \text{and} \quad C_P(t) = TP/Vp(t)$$

thus

$$C_P(t) = C_{Pb}Vpb/Bp(t)$$

and from equation 6

$$C_P(t) = C_{Pb}(Ht(t)/Ht_b)(100 - Ht_b)/(100 - Ht(t)) \quad (7)$$

Ht_b; Ht before hemodialysis

Calculation of Kr

Since the change in $V_P(t)$ is calculated from the changes in the hematocrit, $V_P(t)$ can be fitted by regression analysis to an exponential curve and expressed by

$$V_P(t) = B\, e^{(At)} \quad (8)$$

where A and B are constants. Differentiating this equation gives

$$dV_P(t)/dt = AB\, e^{(At)} \quad (9)$$

and by substituting equations 9 and 5 into equation 1 we obtain

$$AB\, e^{(At)} = Kr(t)(\pi p(t) - \pi p(0)) - Uf$$

In this equation, A and B are obtained from equation 8, and $\pi p(t)$ and $\pi p(0)$ are obtained from equations 3 and 7. From these assumptions, Kr is expressed by

$$Kr(t) = [AB\, e^{(At)} + Uf]/[\pi p(t) - \pi p(0)]$$

Thus Kr can be calculated from measurements of the hematocrit, total serum protein before hemodialysis, the water removal rate, and changes in body weight.

In the above calculation of Kr, we assumed that Pc, Pi and πi are constant during hemodialysis. However, water removal results in lowered blood pressure and subsequent hormonal changes which might induce changes in Pc, Pi and πi. To determine how changes of these parameters affect the calculated value of Kr, we recalculated Kr, changing the individual parameters.

The main determinants of intracapillary hydrostatic pressure, Pc are P_A, the intracapillary hydrostatic pressure at the arterial ends of the capillaries, and P_V, the intracapillary hydrostatic pressure at the venous ends of the capillaries, Pc can be expressed by the following equation [5],

$$P_C = [P_A(R_V/R_A) + P_V]/[1 + (R_V/R_A)]$$

where R_V is the capillary resistance at the venous ends and R_A is the capillary resistance at the arterial ends. However, we cannot measure these parameters directly in the patients. In previous experiments, the intracapillary hydrostatic pressure at the arteriolar end of human skin was 30.6–34.3 mm Hg [6–8], and that at the venous end was 12.1–21.9 mm Hg [6–8]. We used the averages of these measurements as stated in Landis and Pappenheimer [5], in our calculation of Kr, P_A = 32 mm Hg, P_V = 15 mm Hg, and R_V/R_A = 0.25. Using these estimated values, P_C was calculated to equal 18.4 mm Hg. Assuming that the protein concentration of the interstitial fluid was zero, and using the value of Pc and $\pi p(0)$, πi could then be calculated from equation 4.

Fleming et al. [9] have shown that the erythrocyte volume changes with the sodium concentration of the dialysate, which suggests that the blood volume calculated from hematocrit may not always coincide with the true blood volume during hemodialysis, especially in the late phase of hemodialysis when osmolytes including urea are dialyzed and the plasma osmolarity changes. To address this question we compared Kr calculated from the hematocrit with Kr calculated from the plasma protein concentration under the assumption that the total protein content was preserved during a single session of hemodialysis. The average value of Kr (n = 11) calculated from the hematocrit was 225.9 ± 45.3 ml/mm Hg/h, and from the protein concentration was 229.0 ± 48.7 ml/mm Hg/h. Regression analysis revealed a significant linear correlation between values calculated by the two methods (r = 0.997). Furthermore, in our study the sodium concentration of the dialysate was 140 mEq/l, which would cause only a very small change in erythrocyte volume [9]. Therefore we used the hematocrit values to calculate Kr in the present study.

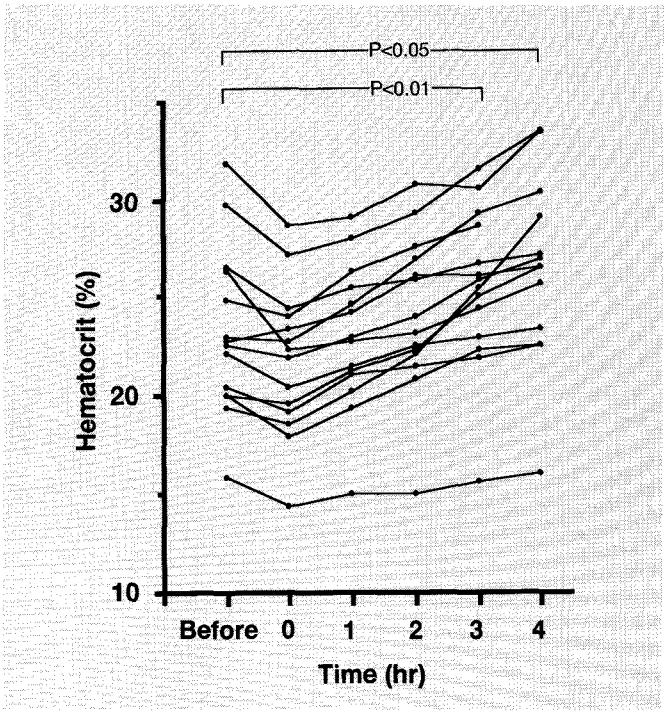

Fig. 1. Changes in hematocrit during hemodialysis. Hematocrits were obtained before hemodialysis began, before the start of water removal, and 1, 2, 3 and 4 h into the dialysis session. The hematocrit was lower just before the start of water removal than before the session started due to hemodilution caused by priming saline infusion (200 ml). Subsequently the hematocrit increased gradually during water removal.

Hematocrits were measured using a Sysmex Auto Blood-Cell Counter CCC-180 (Toa Medical Electronics Co., Kobe, Japan). The reliability of this method is extremely high, and the error in Ht was <0.1%.

Statistics

Data are expressed as the mean ± SE. Statistical comparisons between groups were made by analysis of variance and Scheffé's post hoc comparison. Differences were considered significant for $p < 0.05$.

Results

For 14 hemodialysis patients the volume of water removed during a single hemodialysis session was 2,692 ± 219 ml (range 1,400–4,200), at the rate of 710 ± 50 ml/h. As the water was removed, the circulating blood was concentrated and the hematocrit gradually increased (fig. 1). The hematocrit before hemodialysis began was

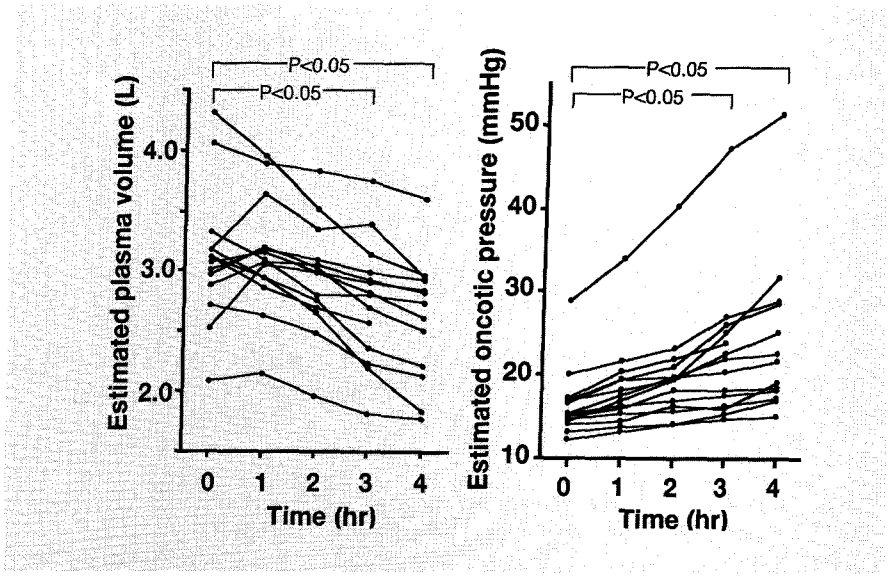

Fig. 2. Changes in the estimated plasma volume and oncotic pressure during hemodialysis. The estimated plasma volume was calculated from the changes in the hematocrit, using equation 7. The plasma volume decreased gradually during water removal. The intracapillary oncotic pressure was calculated from the estimated changes in the total serum protein as described in the text and increased gradually during water removal.

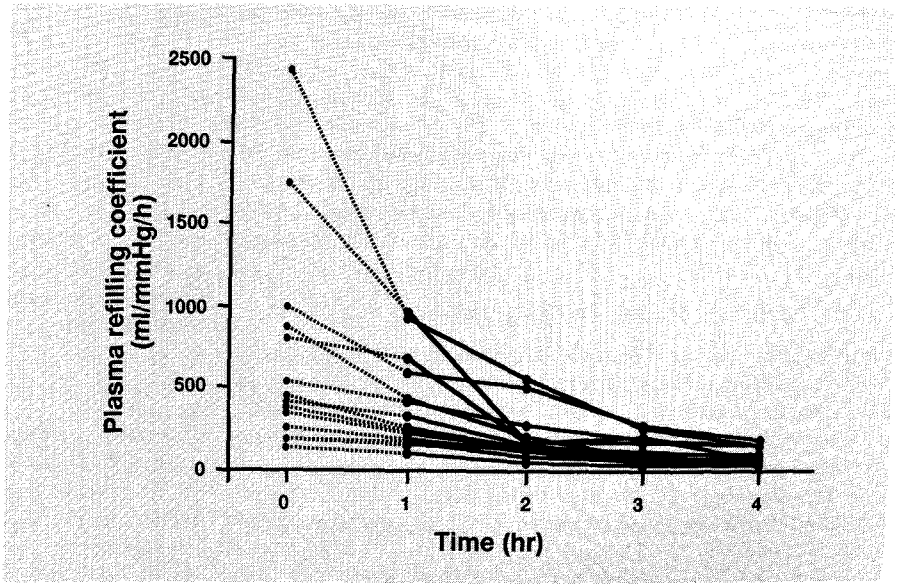

Fig. 3. Changes in the calculated plasma-refilling coefficient, Kr, during hemodialysis. The plasma-refilling coefficient decreased markedly during water removal, although the driving force pulling water into the capillaries increased as a result of hemoconcentration. Dotted lines denote the calculated plasma-refilling coefficient fitted exponentially to the data for each time point.

23.3 ± 1.1%, but infusion of the priming saline diluted the blood and the hematocrit had decreased slightly to 21.8 ± 1.0%. One hour into the session the hematocrit was 23.0 ± 1.0 and it continued to increase gradually thereafter: 2 h, 24.2 ± 1.1%; 3 h, 25.5 ± 1.1% ($p < 0.01$ vs. before), and 4 h, 26.5 ± 1.3% ($p < 0.05$ vs. before hemodialysis). The estimated oncotic pressure before hemodialysis was 18.7 ± 1.5 mm Hg, as the total serum protein concentration was 5.5 ± 0.3 g/dl. As water was removed, the total serum protein became more concentrated, and the calculated intracapillary oncotic pressure increased (fig. 2) from 21.1 ± 1.9 mm Hg after 1 h to 23.5 ± 2.6 mm Hg (2 h), 26.9 ± 3.4 mm Hg (3 h, $p < 0.01$ vs. before hemodialysis) and 27.8 ± 4.5 mm Hg (4 h, $p < 0.05$ vs. before hemodialysis). At the same time, the estimated plasma volume decreased gradually as water was removed (fig. 2). The plasma volume before hemodialysis was 3.37 ± 0.14 liters, and it decreased to 3.13 ± 0.13 liters (1 h), 2.94 ± 0.12 liters (2 h), 2.76 ± 0.13 liters (3 h, $p < 0.01$ vs. before), and 2.61 ± 0.14 liters (4 h, $p < 0.05$ vs. before hemodialysis). These parameters were used to calculate the plasma-refilling coefficient, Kr, which decreased gradually as water was removed (fig. 3). The average Kr for 14 patients was 405.3 ± 75.4 ml/mm Hg/h 1 h

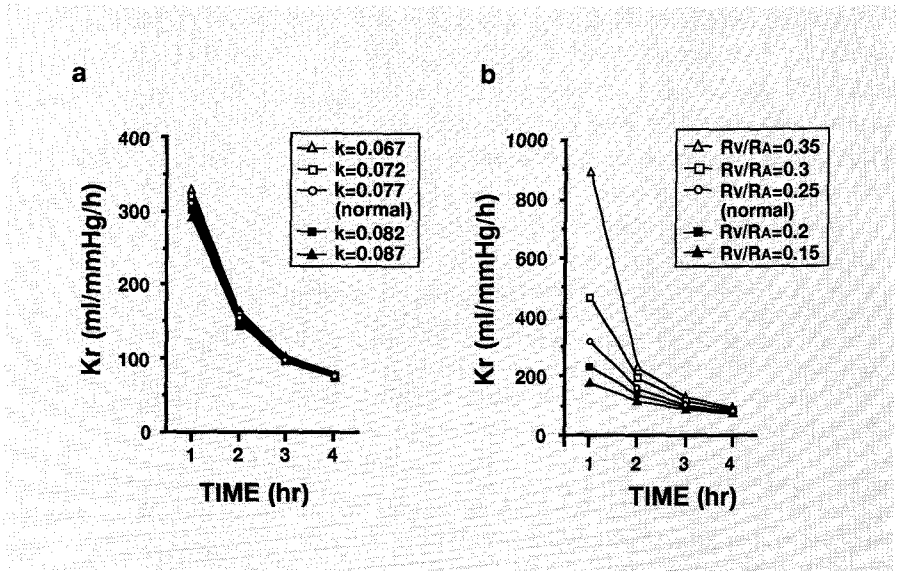

Fig. 4. Effects on the plasma-refilling coefficient, Kr, of changing by varying the percentage estimated circulating blood volume to body weight, and vascular resistance ratios. **a** In calculating Kr, the circulating blood volume was taken as 7.7% of the body weight. Changing the percentage estimated circulating blood volume from 6.7 to 8.7% did not substantially change the calculated value of Kr. **b** We estimated R_A/R_V to be 0.25 and calculated Pc as 18.7 mm Hg. However, when R_A/R_V was taken as 0.15, Pc eas 17.2 mm Hg, and when R_A/R_V was taken as 0.35, Pc was 19.4 mm Hg, and in both cases, Kr varied widely.

into the session, and it decreased to 203.9 ± 39.5 (2 h), 130.2 ± 20.5 (3 h), and 93.9 ± 14.3 (4 h) thereafter. Kr at the beginning of water removal was calculated by regression analysis of the hourly data, and was estimated to be 698.9 ± 175.2 ml/mm Hg/h (range 140.3–1,744).

In the calculation of Kr, we estimated several parameters. If these parameters are changed during hemodialysis, we expect the calculated value of Kr to be affected. To evaluate which factors were important in influencing Kr, we recalculated Kr using different values of each parameter, and using the mean values for body weight, total serum protein, the water removal rate, and changes in the hematocrit, as given above.

We estimated that the circulating blood volume was 7.7% of the body weight. When we varied the estimated circulating blood volume from 6.7 to 8.7% of body weight, there was no substantial change in the calculated value of Kr (fig. 4a). Thus, estimation of the circulating blood volume had a minor influence on this calculation.

We assumed that Pc does not change during water removal, and estimated that P_A was 32.0 mm Hg, P_V was 15 mm Hg, and R_V/R_A was 0.25. Hence we calculated that Pc was 18.4 mm Hg. However, Pc may have changed during hemodialysis. If R_A/R_V was 0.15, the calculated value of Pc would be 17.2 mm Hg, and Kr would be lower than that for $R_A/R_V = 0.25$. Conversely, if R_A/R_V was 0.35, Pc would be 19.4 mm Hg and Kr would be higher than for $R_A/R_V = 0.25$ (fig. 4b).

We also assumed that P_A does not change during water removal, and estimated that P_V was 32.0 mm Hg. However, if P_A decreased during water removal at the rate of 1 mm Hg/h (from 32 mm Hg at the beginning of water removal to 28 mm Hg after 4 h), 2 mm Hg/h (32–24 mm Hg), or 4 mm Hg/h (32–16 mm Hg), Pc would also decrease, from 18.4 mm Hg at the beginning of water removal to 17.8, 14.8 or 8.8 mm Hg at the end of hemodialysis in each given changes in P_A. Under these conditions, Kr would be slightly lower than that if Pc was constant during hemodialysis (fig. 5a).

We also assumed that P_V did not change during water removal, and estimated that P_V was 15 mm Hg. However, if P_V decreased during water removal at the rate of 1 mm Hg/h (from 15.0 mm Hg at the beginning of water removal to 11 mm Hg after 4 h), 2 mm Hg/h (15–7 mm Hg), or 3 mm Hg/h (15–3 mm Hg), Pc would also decrease from 18.4 mm Hg at the beginning to 15.2, 12.0 or 8.8 mm Hg at the end of hemodialysis in each given changes in P_V. Under these conditions, Kr would be lower than if Pc was constant during hemodialysis (fig. 5b).

Finally, if P_A decreased at a rate of 2 mm Hg/h (32 mm Hg at the beginning and 24 mm Hg after 4 h), 4 mm Hg/h (32–16 mm Hg) or 6 mm Hg/h (32–8 mm Hg), and at the same time P_V decreased at a rate of 1 mm Hg/h (15–11 mm Hg), 2 mm Hg/h (15–7 mm Hg), or 3 mm Hg/h (15–3 mm Hg), Pc would decrease from 18.4 mm Hg at the beginning to 13.6, 8.8 or 4.0 mm Hg at the end of hemodialysis in each given changes in P_A and P_V. Under these conditions, Kr would be much lower than if Pc is constant during hemodialysis (fig. 6).

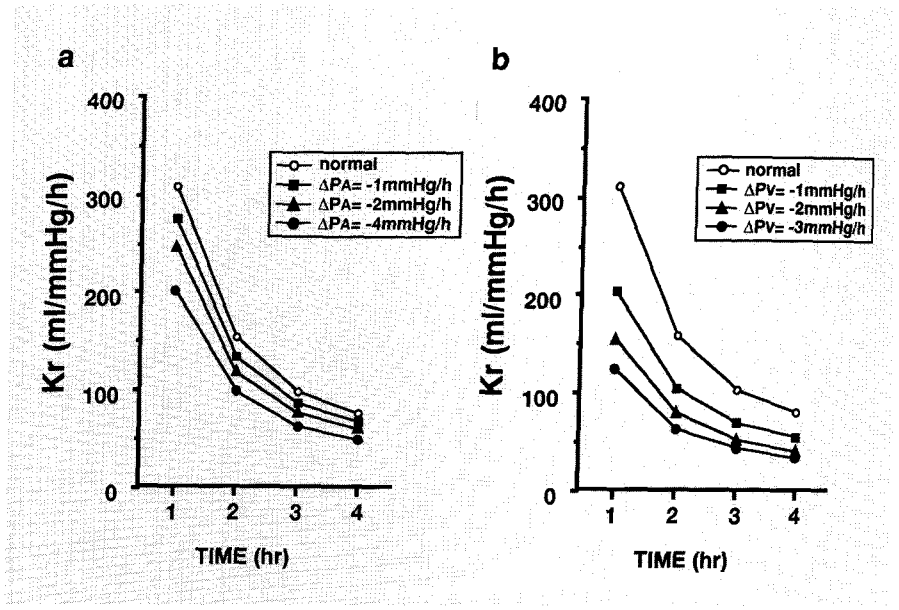

Fig. 5. Effects on the plasma-refilling coefficient, Kr, of various hydrostatic pressures at the arteriole and venous ends of the capillaries. **a** When P_A was decreased at a rate of 1, 2 or 4 mm Hg/h during water removal, the calculated value of Kr did not change substantially. **b** When P_V was assumed to decrease during water removal at the rate of 1, 2 or 3 mm Hg/h, the calculated value of Kr was lower than when Pc was assumed to be constant during hemodialysis.

Discussion

Hemodialysis is widely used for the treatment of uremia. This procedure effectively removes uremic substances, such as urea nitrogen, creatinine, and protein metabolites from the blood, and also corrects electrolyte imbalance. In addition, hemodialysis also corrects water imbalance in uremic patients; however, some patients experience a marked drop in blood pressure, whereas other patients have stable blood pressure throughout the hemodialysis session. As the estimated circulating blood volume is 7.7% of the body weight, the estimated plasma volume is only 5% of the body weight when the hematocrit is 30%. The average amount of water removed during hemodialysis is about 3–5%. The circulating plasma volume should be maintained by plasma refilling, yet, in most cases, hemodialysis-induced hypotension is caused by a rapid reduction in the circulating blood volume [1]. The process of plasma refilling is driven by the serum protein concentration, which increases during water removal, pulling water from the interstitial space into the circulation. These findings led us to hypothesize that capillary water permeability is low in patients with hypovolemic hypotension that was induced by hemodialysis. However, there is no available index for examining capillary water permeability in hemodialysis patients. Thus we present here a formula for calculating a plasma-refilling coefficient, which is an index of capillary water permeability, from changes in the hematocrit during hemodialysis.

As expected, the value of the plasma-refilling coefficient decreased gradually during hemodialysis, although the intracapillary oncotic pressure, a driving force of plasma refilling, increased due to hemoconcentration (fig. 1–3). Although the mechanism causing this decrese in Kr remains unclear, it should be noted that the calculated value of Kr is the product of capillary water permeability coefficient and the capillary surface area. Therefore, the most likely explanation for the decrease in Kr is that vasoactive substances, such as catecholamines and angiotensin II, induced vasoconstriction. If this was the case, since Kr decreased to one-fifth of its original value (fig. 3), the capillary surface area could also be expected to decrease substantially. To test this thesis, we examined the effect of norepinephrine on Kr in hemodialysis patients [10]. Continuous norepinephrine infusion (0.04 μg/kg/min) during hemodialysis resulted in a small decrease in Kr of 5–10%. Moreover, the plasma concentration of catecholamines and angiotensin II has been reported to be stable, or increase only slightly, during hemodialysis [11]. Therefore, it appears that vasoconstriction induced by catecholamines and angiotensin II was not the main factor which caused the reduction of Kr observed in this study. A second possible mechanism is that vasoactive substances such as atrial natriuretic peptide might decrease the vascular water-permeability coefficient directly. We have previously reported a tight correlation between Kr and the plasma concentration of atrial natriuretic peptide in hemodialysis patients [12]. Thirdly, water

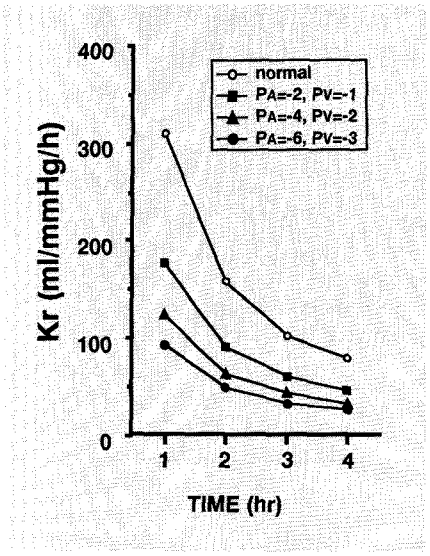

Fig. 6. Effects on the plasma-refilling coefficient, Kr, of various hydrostatic pressures at both the arteriole and venous ends of the capillaries. When P_A was assumed to decrease at a rate of 2, 4 or 6 mm Hg/h whilst P_V also decreased the rate of 1, 2 or 3 mm Hg/h, the calculated value of Kr was lower than when Pc was assumed to be constant during hemodialysis.

removal may change other driving forces, such as the intracapillary hydrostatic pressure, the interstitial hydrostatic pressure, or both. When water is removed by hemodialysis, the intracapillary hydrostatic pressure is expected to decrease, which may cause plasma refilling to accelerate via reduction in the transcapillary hydrostatic pressure gradient. On the other hand, the expected reduction of the interstitial hydrostatic pressure might slow plasma refilling. However, the absolute values of the hydrostatic pressures are very low compared with the increase in oncotic pressure, suggesting that hydrostatic pressure may have only a small influence on plasma refilling. Moreover, Zweifach and Intaglietta [13] reported that in capillaries of omentum and mesentery, the intracapillary pressure remains constant, despite wide variations in arterial pressure.

The influence of the interstitial pressure can be examined using equation 4. Intracapillary pressure, Pc, was estimated to be 18.4 mm Hg. The serum protein concentration of interstitial fluid is 0.7–2.1 g/dl, in human limbs under normal resting conditions [5], and the interstitial pressure in human muscle ranges from 0.7 to 8.9 mm Hg [5]. If the protein concentration of the interstitial fluid was 1.0 g/dl, interstitial oncotic pressure was 2.3 mm Hg and total serum protein before hemodialysis was 7.0 g/dl, the intracapillary oncotic pressure would be calculated to be 22.5 mm Hg, and therefore the estimated interstitial hydrostatic pressure, Pi, would be only 1.8 mm Hg. These values indicate that changes in total serum protein also induce changes in interstitial hydrostatic pressure and the protein concentration of the interstitial fluid. However, during hemodialysis, water removal might cause a drop in interstitial hydrostatic pressure, together with an increase in the protein concentration of the interstitial fluid. Since $\pi p(t) - \pi p(0) = \pi p(t) - \pi i - (Pc - Pi)$, the drop in interstitial hydrostatic pressure and increase in the protein concentration of the interstitial fluid will induce antegrade forces which will minimize the effect on plasma refilling. To clarify the mechanisms reducing Kr, changes in the interstitial hydrostatic pressure and interstitial protein concentration should be measured. However, we do not currently have a convenient method for making these measurements.

Since we estimated several parameters in the calculation of Kr, we evaluated the importance of each estimated parameter. When the estimated circulating blood volume, or the transcapillary pressure gradient at the arteriolar end of the capillaries, $P_C - P_A$, was varied, the calculated value of Kr changed slightly. On the other hand, when the transcapillary pressure gradient at the venous end of the capillaries, $P_C - P_V$, or the transcapillary pressure gradient at both ends, was varied, the calculated value of Kr changed moderately. However, when the ratio of vascular resistance (R_A/R_V) was varied, the calculated value of Kr changed markedly. Although these results indicated that the ratio of vascular resistance was the most important determinant of Kr, the change in vascular resistance results in change in the intracapillary hydrostatic pressure. Moreover, in animal experiments, intracapillary pressure remains constant despite fluctuating arterial pressure [13], indicating that during hemodialysis, water removal may not affect the transcapillary hydrostatic pressure gradient.

We observed that capillary water permeability before hemodialysis was 698.9 ± 15.2 ml/mm Hg/h. If the total surface area of the vascular bed was about 100 m^2 in humans [14], the capillary water-permeability coefficient in hemodialysis patients was 0.18 nl/s/mm Hg/cm^2. From animal experiments, the vascular water permeability has been determined for: rabbit omentum at the arterial end, 0.15–0.59 nl/s/mm Hg/cm^2 [15]; the rabbit cremaster muscle, 0.74 nl/s/mm Hg/cm^2 [16]; guinea pig mesentery, 1.25 nl/s/mm Hg/cm^2 [17], and cat mesentery, 0.45 nl/s/mm Hg/cm^2 [18]. By contrast, that of rat glomerular capillaries is 41 nl/s/mm Hg/cm^2 [19]. Thus the value of

0.18 nl/s/mm Hg/cm^2 for hemodialysis patients presented here is consistent with previously reported value of hydraulic conductivity, although the estimated total vascular surface area is unknown.

These findings indicate that changes in intracapillary hydrostatic pressure during water removal affect the estimated value of Kr, however, the transcapillary hydrostatic pressure gradient and the estimated circulating plasma volume (as a percentage of body weight) are not as important in calculating Kr.

We conclude that the formula proposed in this paper for calculating the plasma-refilling coefficient is a convenient and useful index for examining plasma refilling in hemodialysis patients.

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