Kidney International, Vol. 42 (1992), pp. 1425–1433

Nature and rate of vascular refilling during hemodialysis and ultrafiltration

DANIEL SCHNEDITZ, JOHANNES ROOB, MARTINA OSWALD, HELMUTH POGGLITSCH, MAXIMILIAN MOSER, THOMAS KENNER, and ULRICH BINSWANGER

Department of Physiology, Karl-Franzens University, Labor für Meßtechnik, Dr. Stabinger, and Division of Nephrology, Department of Internal Medicine, School of Medicine, Graz, Austria; and Division of Nephrology, Department of Internal Medicine, University Hospital Zürich, Switzerland

Nature and rate of vascular refilling during hemodialysis and ultrafiltration. The change of blood volume, of blood and plasma density (ρ_b, ρ_p) following a short ultrafiltration pulse (duration: 20 min; mean rate −35 ml/min) within the first hour of hemodialysis was analyzed in 13 hemodynamically stable patients (30 single measurements). Protein concentration of refilling volume (7 g/liter) was calculated from its density (1009.25 ± 3.7 kg/m^3, at 20°C) and from the linear relationship between plasma density and protein concentration (c_p) of uremic plasma samples ($\rho_p = 1007.46 + 0.2422 \times c_p$). The filtration coefficient ($L_{p,calc}$) determined from a relation derived from Starling's hypothesis was 5.6 ± 1.4 ml/(min · mm Hg · 50 kg lean body mass); $N = 13$, mean ± SD, minimum 3.2, maximum 8.0. A model describing the dynamics of blood and plasma volume was developed. It was fit to on-line measurements of relative blood volume changes by variation of the filtration coefficient and of initial blood volume ($L_{p,fit}$, $V_{b,fit}$). The linear regression between $V_{b,fit}$ and blood volume determined from anthropometry ($V_{b,calc}$) was highly significant ($r = 0.79$, $N = 30$, $P < 0.001$). Compared to $V_{b,calc}$, $V_{b,fit}$ was typically increased by 21 ± 11%, reflecting a fluid overload at the beginning of the treatment. $L_{p,fit}$ was not different from $L_{p,calc}$. $L_{p,fit}$ significantly increased with blood volume excess. Due to the small but definite protein content of refilling volume, the model accounts for increased blood volume recovery and occasional overshoot of blood and plasma volumes following ultrafiltration.

Hemodialysis generally includes ultrafiltration in order to remove accumulated body water from the patient. After removal of fluid from the circulating blood volume by ultrafiltration, refilling occurs from the extravascular compartment. This together with other compensatory mechanisms such as decreasing venous capacitance, increasing cardiac contractility and rate, and increasing vascular resistance, helps to preserve blood pressure and tissue perfusion [1, 2]. However, inadequate refilling will lead to hypovolemia which is suspected to be a major cause for hemodialysis related hypotension [3].

The redistribution of fluid between the extravascular compartment and the blood volume is modulated by the composition of vascular refilling volume. The change in colloid-osmotic pressures in the extravascular space and in blood not only depends on pure fluid shifts, it also depends on the flow of colloid-osmotic active components between the two compartments. Since fluid refilling from the extravascular space into the vascular compartment is not accessible to direct investigation, it is not surprising that a variety of estimates concerning its protein content has been presented. The question has been dealt with in different experimental studies including hemodilution, hemorrhage or plasmapheresis in animals [4–6] and after changes in body position or ultrafiltration treatment in humans [7, 8]. Estimates for protein concentration of refilling volume range from protein-free and protein-poor (<1 g/liter) [9] to protein-rich (≈25 g/liter) [5], the latter reflecting one-third to one-half of the average plasma protein concentration.

Vascular refilling depends on treatment modes such as ultrafiltration rates and on patient parameters such as body size, fluid overload, plasma volume, regional blood flow distribution, plasma protein concentration and transcapillary pressure gradients. Because of this complex interdependence, and in order to obtain refilling data which are more comparable among patients and treatment modes, blood volume changes have to be studied in relation to as many of these parameters as possible.

In this paper, vascular refilling is described in terms of filtration coefficients (L_p). The study consisted of a short ultrafiltration phase done early in treatment, and an analysis of vascular refilling with respect to its protein content and to its filtration coefficient. The experimental data were fit to a kinetic model to obtain model parameters which were related to fluid overload.

Methods

Thirteen stable patients (5 men and 8 women) who had been dialyzed for 2 to 159 months (mean duration: 60 months) participated in the study. The age range was 28 to 63 years (mean age: 49 years). GFE-18 dialyzers and AK-100 Dialysis-Monitors (Gambro AB, Lund, Sweden) and F80 or F60 dialyzers and A2008-C Dialysis Monitors (Fresenius AG, Bad Homburg, Germany) were used to perform the treatments. Dialysate contained acetate as base and Na^+ in a concentration of 137 mEq/liter. Mean blood and dialysate flows were 200 ml/min and 500 ml/min, respectively. Treatment time was three to eight hours (mean treatment time: 5 hr 15 min).

Ultrafiltration was set to achieve previously clinically determined "dry weight". Total treatment ultrafiltration averaged

Received for publication April 8, 1992
and in revised form June 15, 1992
Accepted for publication July 13, 1992

3.6 ± 2.1 liter. Fluid removal was equally divided among each treatment hour. Measurements of blood and plasma densities (ρ_b, ρ_p) were performed only during the first 60 minutes of the treatment. Ultrafiltration during this experimental period, unlike other periods, was varied. No fluid was removed during the first 20 minutes (equilibration phase) or the last 20 minutes (recovery phase) of the experimental period. However, the entire hourly volume of fluid to be removed was removed in toto during the middle 20 minutes (ultrafiltration phase) of the experimental period. Therefore, the fluid loss in the experimental period was the same as in comparable time periods during the remainder of the treatment. With four exceptions where the removal of fluid was achieved by pure ultrafiltration the study was done concomitantly with dialysis.

Patients were supine for 20 minutes prior to and during the treatment. Food or fluids were not ingested during the treatment. Hemodynamically unstable patients or patients taking vasoactive drugs were excluded from the study. Informed consent was obtained from all patients.

Measurements

Blood samples from the arterial limb of the extracorporeal circulation were taken at 20, 40 and 60 minutes. Hematocrit (Hct) determined by centrifugation was corrected for trapped plasma and for non-uniform distribution of red cells within the circulatory system [10] ($Hct = Hct_{centrifuge} \times 0.97 \times 0.81$). Plasma protein concentration (c_p, g/liter) was determined by the Biuret method.

Plasma density (ρ_p in kg/m^3, at 20°C) was determined by a mechanical oscillator technique (DMA-602 MW, A. Paar K.G., Graz, Austria) [11] and blood density (ρ_b) was determined from continuous, on-line measurement of sound speed in blood (Ultrasonic Blood Monitor, A. Paar K.G., Graz, Austria) [12, 13].

Analysis

Density of refilling volume (ρ_{ref}). Density of refilling volume was calculated from blood and plasma densities (ρ_b, ρ_p) determined at the beginning (index 1) and at the end (index 2) of the 20-minute recovery phase where no ultrafiltration had taken place, as well as from the hematocrit at the beginning of this phase [14] (**Appendix A**):

$$\rho_{ref} = \frac{\Delta\rho_b \times \rho_{p2} - \Delta\rho_p \times \rho_{b2} \times (1 - Hct_1)}{\Delta\rho_b - \Delta\rho_p \times (1 - Hct_1)} \quad \text{(Eq. 1)}$$

$\Delta\rho_b$ is ($\rho_{b1} - \rho_{b2}$) and $\Delta\rho_p$ is ($\rho_{p1} - \rho_{p2}$), respectively. The accuracy for the calculation of ρ_{ref} for a 5% blood volume change was in the range of ±1.5 kg/m^3.

Relative change of blood volume ($\Delta V_b/V_{b1}$). Relative change of blood volume for any phase of the experimental period was calculated from initial hematocrit and from the change of blood and plasma densities (ρ_p, ρ_b) (**Appendix B**):

$$\frac{\Delta V}{V_{b1}} = \frac{\Delta\rho_p \times (1 - Hct_1) - \Delta\rho_b}{\rho_{b2} - \rho_{p2}} \quad \text{(Eq. 2)}$$

Filtration coefficient (L_p). The change of plasma volume (ΔV_p) within a period of time (t) is given by the refilling flow (J_{REF}) and the ultrafiltration rate (J_{UF}):

$$\frac{\Delta V_p}{t} = J_{REF} + J_{UF} \quad \text{(Eq. 3)}$$

Refilling flow, as described by Starling's hypothesis, is proportional to transmural hydrostatic (Δp) and colloid-osmotic ($\Delta\pi$) pressure gradients:

$$J_{REF} = L_p \times (\Delta\pi - \Delta p). \quad \text{(Eq. 4)}$$

L_p is the filtration coefficient.

The following simplification was made for further calculation: transmural hydrostatic pressure gradients as well as interstitial colloid-osmotic pressures (π_i) remain unchanged ($\Delta p = 0$, π_i = const.) during the experimental period so that

$$J_{REF} = L_p \times (\pi_{p2} - \pi_{p1}). \quad \text{(Eq. 5)}$$

($\pi_{p2} - \pi_{p1}$) refers to the change in plasma colloid-osmotic pressure during the experimental period. With (Eq. 5) the change of plasma volume is then given as

$$\frac{\Delta V_p}{t} = J_{UF} + L_p \times (\pi_{p2} - \pi_{p1}). \quad \text{(Eq. 6)}$$

Blood volume (V_b) at the beginning of the treatment was estimated from lean body mass (LBM) as described elsewhere [15]. The change of plasma volume (ΔV_p) was then calculated from blood volume changes (Eq. 2) and from initial hematocrit. L_p was normalized to a LBM of 50 kg.

Dynamics of blood and plasma volume during ultrafiltration. The assumptions for the open, two compartment kinetic model were as follows (Fig. 1):

(1) The plasma compartment (V_p) is open at the dialyzer membrane where protein-free ultrafiltrate is removed by ultrafiltration. It is connected to the interstitial compartment (V_i) in the microvasculature.
(2) Flow across the dialyzer membrane (J_{UF}) is determined by ultrafiltration rate as set at the dialysis machine.
(3) Refilling flow (J_{REF}) between V_p and V_i is determined by the transmural colloid-osmotic pressure gradient ($\Delta\pi$) and by (L_p) (Eq. 5).
(4) Protein backflow (J_{Prot}) is determined by protein concentration in refilling fluid ($c_{ref} \approx 7$ g/liter) and by refilling flow ($J_{Prot} = J_{REF} \times c_{ref}$).
(5) Initial interstitial protein concentration (c_i) equals one-third of the intravascular protein concentration (c_p).
(6) Initial V_i equals three times V_p.

The system of differential equations to describe the dynamics of plasma volume is derived in **Appendix C**. Model parameters for the filtration coefficient and for the initial blood volume were varied to fit experimental data.

Results

Mean ultrafiltration volume during the experimental period was 0.73 liter, which referred to a net fluid loss of approximately −14% of the calculated initial blood volume (Table 1). However, due to vascular refilling of 0.32 liter during this phase, the relative blood volume decrease was only −7.5%. Refilling was 0.22 liter during the subsequent ultrafiltration-free recovery phase. At the end of the experimental period 74% of

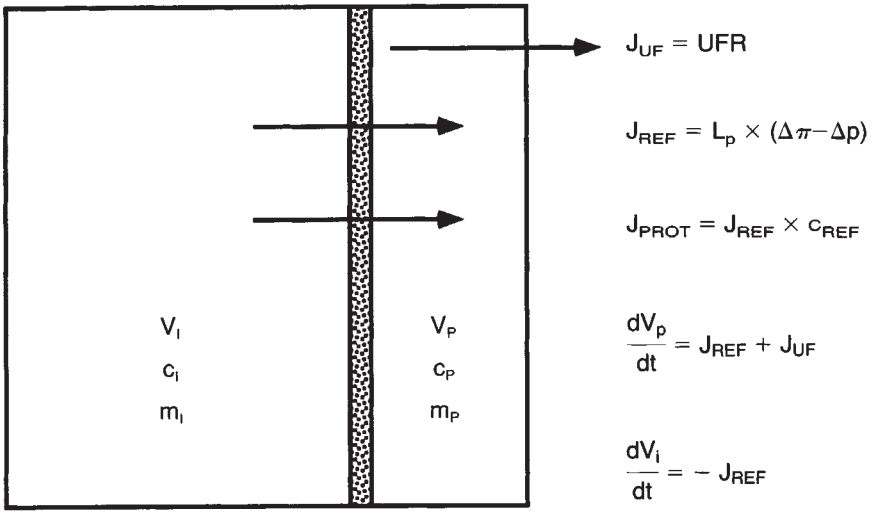

Fig. 1. *Open, two-compartment model.* Volumes (V), protein masses (m) and protein concentrations (c) of the plasma (index p) and interstitial (index i) compartments are assumed to depend on the following flows: ultrafiltration flow (J_{UF}), refilling flow (J_{REF}) and protein refilling flow (J_{Prot}). The barrier between the two compartments has a limited protein permeability.

Table 1. Mean ultrafiltration (UF) and refilling data (13 patients and 30 studies)

Patient	N	Body wt	LBM	V_b	UFV_{total}	$UFV_{exp't}$	J_{UF}	$V_{ref,UF}$	$V_{ref,REF}$	$\Delta V/V_{UF}$	$\Delta V/V_{REF}$
		kg		*liter*			*ml/min*	*liter*		*%*	
HaMa	(3)	55.5	45.2	4.6	3.2	0.80	−40.0	0.48	0.23	−7.0	5.3
HeGe	(2)	70.0	46.0	4.7	3.3	0.73	−36.4	0.27	0.28	−9.7	6.6
HeSo	(3)	50.2	41.0	4.2	3.8	0.64	−31.9	0.23	0.25	−9.7	6.5
HiMa	(3)	70.5	47.5	4.9	2.9	0.64	−31.9	0.27	0.24	−7.6	5.4
SaWi	(3)	109.0	71.1	7.1	7.5	1.08	−53.8	0.46	0.31	−8.7	4.8
ScJo	(5)	63.7	51.1	5.2	3.5	0.43	−21.7	0.23	0.16	−3.9	3.3
WaHi	(4)	50.3	41.5	4.3	4.0	0.94	−46.8	0.41	0.20	−12.3	5.3
WiKa	(2)	75.0	57.8	5.8	7.4	0.97	−48.6	0.40	0.31	−9.8	5.9
WoAn	(1)	66.0	55.2	5.6	4.4	0.93	−46.7	0.36	0.23	−10.2	4.5
FrSu[a]	(1)	57.0	47.4	4.8	1.2	0.40	−20.0	0.22	0.21	−3.7	4.5
LeTe[a]	(1)	70.0	48.8	5.0	1.8	0.47	−23.3	0.23	0.10	−4.7	2.2
GrVe[a]	(1)	71.0	53.3	5.4	2.3	0.60	−30.0	0.39	0.15	−3.9	2.9
GaGi[a]	(1)	90.5	63.6	6.4	2.2	0.60	−30.0	0.21	0.23	−6.1	3.8
Mean		69.1	51.5	5.2	3.6	0.73	−35.5	0.32	0.22	−7.5	4.7
SD		15.9	8.2	0.8	2.1	0.26	11.0	0.09	0.06	2.9	1.1
Minimum		50.2	41.0	4.2	1.2	0.33	−53.8	0.21	0.10	−12.3	2.2
Maximum		109.0	71.1	7.1	7.5	1.16	−20.0	0.48	0.31	−3.7	6.6

Abbreviations are: number of studies done with the same patient (*N*); dry body weight (Body wt); lean body mass (LBM); blood volume calculated from LBM ($V_{b,calc}$); UF volume during total treatment (UFV_{total}); UF volume during experimental period ($UFV_{exp't}$); UF rate during experimental period (J_{UF}); refilling volume during UF phase ($V_{ref,UF}$) and during refilling phase ($V_{ref,REF}$); relative change of blood volume during UF phase ($\Delta V/V_{UF}$) and during refilling phase ($\Delta V/V_{REF}$).

[a] Studies done with pure ultrafiltration

the fluid removed by ultrafiltration had been refilled from the extravascular space. The ultrafiltration procedure was well tolerated by the patients and systolic blood pressure changes during the experimental period were less than 20 mm Hg. With high hematocrits and high ultrafiltration rates, transmembrane pressures in the dialyzer reached 400 mm Hg, but remained below the safety limit given by the manufacturers (500 mm Hg).

Both blood and plasma densities increased in the ultrafiltration phase and decreased in the recovery phase (Table 2). This was related to corresponding changes in plasma protein concentrations and hematocrits (Table 3). A representative on-line measurement of blood density by ultrasonic technique in the arterial line of the extracorporeal circulation is shown in Figure 2.

Density of refilling volume (ρ_{ref}, Eq. 1) for the recovery phase was 1009.3 ± 3.8 kg/m^3 (at 20°C). Its protein concentration of $c_{ref} \approx 7$ g/liter was then estimated from the linear relation between plasma density (ρ_p) and protein concentration (c_p) of uremic plasma samples ($\rho_p = 1007.46 + 0.2422 \times c_p$; Fig. 3).

The mean filtration coefficient ($L_{p,calc}$, Eq. 6) calculated for both the ultrafiltration and the recovery phases was 5.6 ± 1.4 ml/(min · mm Hg · 50 kg LBM), Table 4. The filtration coefficient for the ultrafiltration phase was not significantly different from the one for the refilling phase. Neither was there a significant difference between calculated filtration coefficients and fitted filtration coefficients ($L_{p,fit}$) obtained by fitting on-line measurements of relative blood volume changes to the kinetic model. A representative fit describing the dynamics of blood volume during the ultrafiltration phase and the following recovery phase is shown in Figure 4. Initial blood volumes obtained

Table 2. Plasma (ρ_p), blood (ρ_b) and refilling (ρ_{ref}) densities at 20°C in [kg/m^3]

	ρ_p Before	After	End	ρ_b Before	After	End	ρ_{ref}
Mean	1024.42	1026.21	1025.20	1042.78	1045.67	1044.00	1009.25
SD	1.15	1.25	1.21	2.56	2.68	2.65	3.70
Minimum	1021.82	1023.02	1022.48	1037.05	1039.33	1037.65	1001.58
Maximum	1025.84	1028.22	1027.05	1050.07	1055.73	1052.03	1015.82

The samples were taken before and after ultrafiltration and at the end of the refilling phase. ρ_{ref} for refilling in the recovery phase was calculated from (Eq. 1); (N = 30).

Table 3. Plasma protein concentrations (c_p in [g/liter]) and hematocrits (Hct in [%])

	c_p Before	After	End	Hct Before	After	End
Mean	68.9	75.1	71.6	27.9	30.3	29.1
SD	4.0	4.3	4.2	3.1	3.3	3.3
Minimum	59.9	64.1	62.2	19.2	19.6	19.3
Maximum	73.8	82.1	78.0	37.0	40.6	38.5

The samples were taken before and after ultrafiltration and at the end of the refilling phase; (N = 30).

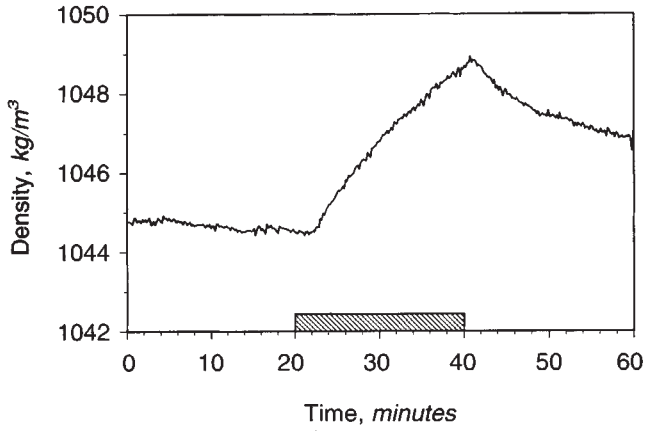

Fig. 2. *Response of blood density (ρ_b) to ultrafiltration profile.* Representative on-line registration of ρ_b in the arterial blood line of the extracorporeal circulation by ultrasonic technique. The ultrafiltration phase is indicated by the bar. (WoAn, J_{UF} = −46.7 ml/min, dry weight = 66 kg, L_p = 3.1 ml/(min · mm Hg 50 kg LBM), ρ_{ref} = 1007.8 kg/m^3).

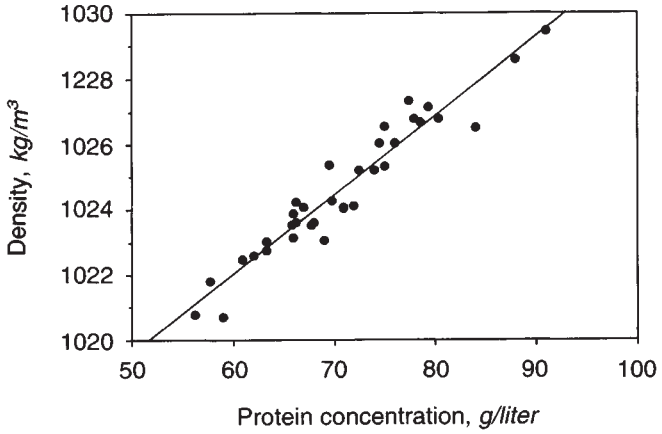

Fig. 3. *Plasma density (ρ_p) versus plasma protein concentration (c_p).* The linear relation between ρ_p and c_p was determined by a least squares fit: ρ_p = 1007.46 + 0.2422 × c_p, r = 0.96. Compared to [16] the slope of the linear regression is decreased whereas its intercept which refers to the density of ultrafiltrate is increased.

to fit the kinetic model ($V_{b,fit}$) were generally larger than blood volumes calculated from anthropometry ($V_{b,calc}$). However, the linear regression between $V_{b,fit}$ and $V_{b,calc}$ ($V_{b,fit}$ = −0.08 + 1.25 × $V_{b,calc}$, r = 0.79, N = 30, P < 0.001) was highly significant. The mean blood volume excess, determined as the relative difference of calculated (from anthropometry) and fitted (from kinetic model) blood volumes ($\Delta V_b/V_{b,calc}$), was 21 ± 11%. The filtration coefficient ($L_{p,fit}$) significantly increased as the blood volume excess ($\Delta V_b/V_{b,calc}$) increased ($L_{p,fit}$ = 3.95 + 0.07 × $\Delta V_b/V_{b,calc}$, r = 0.51, N = 30, P < 0.01).

Finally, summarizing all measurements, the mean change of blood volume for all investigations was calculated by the kinetic model (Fig. 5). To show the overshoot of vascular refilling which would have been attained with colloid-osmotic equilibrium the calculation was extrapolated for a prolonged ultrafiltration-free phase.

Discussion

The composition of refilling volume regarding its protein content and the filtration coefficient for the flow refilling into the intravascular compartment during and following a short ultrafiltration step was analyzed in 13 dialysis patients.

Composition of refilling volume

The protein content of refilling volume was estimated from density measurements. Density of refilling volume (1009.3 kg/m^3) was well above (P < 0.05, t-test) the density of ultrafiltrate (P_{UF}) determined in this study (P_{UF} = 1007.46 kg/m^3, extrapolated to c_p = 0 from the linear relation in Fig. 3) and was significantly higher (P < 0.001, t-test) than the density of ultrafiltrate for normal subjects (P_{UF} = 1005.2 kg/m^3 at 20°C [16]). Density of refilling volume represented a mean for the experimental period. The corresponding protein concentration (7 g/liter) fits a preliminary result obtained in a different experimental setup for an ultrafiltration phase of four to six hours [17]. What is the origin of protein refilling and how can it be explained? From the amount of refilling flow (0.22 liter/20 min during ultrafiltration, Table 1) the additional protein backflow into the vasculature may be assumed to be in the range of 7 × 0.22/20 ≈ 80 mg/min. Part of this additional protein backflow could arise from an increase in lymph flow: with a lymph protein concentration of 20 g/liter and a lymph flow of 2 ml/min, baseline lymph-protein backflow is approximately 40 mg/min [18, 19]. To account for backflow of additional 80 mg/min,

Table 4. Calculated and fitted data (13 patients and 30 studies)

Patient	*N*	$L_{pUF,calc}$	$L_{pREF,calc}$	$L_{p,calc}$ ± SD	$L_{p,fit}$ ± SD	$V_{b,calc}$ *liter*	$V_{b,fit}$ *liter*	$\Delta V/V_{fit}$ %
HaMa	(3)	7.6	5.8	6.7 ± 0.9	7.1 ± 0.1	4.6	6.5	40
HeGe	(2)	4.3	6.8	5.5 ± 1.8	5.4 ± 1.6	4.7	5.4	15
HeSo	(3)	2.7	3.7	3.2 ± 1.3	3.6 ± 0.9	4.2	3.9	−7
HiMa	(3)	4.9	7.0	6.0 ± 2.1	6.0 ± 1.7	4.9	5.4	11
SaWi	(3)	5.5	6.4	5.9 ± 1.9	4.9 ± 0.6	7.1	8.9	25
ScJo	(5)	7.3	6.8	7.0 ± 2.3	7.9 ± 2.1	5.2	7.1	37
WaHi	(4)	4.9	4.6	4.8 ± 1.2	4.0 ± 0.4	4.3	5.9	37
WiKa	(2)	4.1	6.1	5.1 ± 1.2	3.9 ± 0.4	5.8	7.2	23
WoAn	(1)	3.1	4.3	3.7	3.6	5.6	6.5	16
FrSu[a]	(1)	6.7	8.5	7.6	9.0	4.8	5.5	14
LeTe[a]	(1)	3.3	4.8	4.0	3.0	5.0	6.7	35
GrVe[a]	(1)	8.6	7.3	8.0	8.4	5.4	7.0	30
GaGi[a]	(1)	2.0	7.5	4.7	2.5	6.4	6.5	2
Mean		5.0	6.1	5.6 ± 1.6	5.3 ± 1.0	5.2	6.3	21
SD		1.9	1.3	1.4	2.2	0.8	1.0	11
Minimum		2.0	3.7	3.2 ± 0.9	2.5 ± 0.1	4.2	3.9	−7
Maximum		8.6	8.5	8.0 ± 2.3	9.0 ± 2.1	7.1	8.9	40

Abbreviations are: number of studies done with the same patient (*N*); L_p during UF phase ($L_{pUF,calc}$), during refilling phase ($L_{pREF,calc}$) and for both phases ($L_{p,calc}$ ± SD) calculated from (Eq. 6); L_p ($L_{p,fit}$ ± SD) and blood volume ($V_{b,fit}$) determined from kinetic model fit; relative difference between fitted ($V_{b,fit}$) and calculated ($V_{b,calc}$) blood volume ($\Delta V/V_{fit}$).

[a] Studies done with pure ultrafiltration.

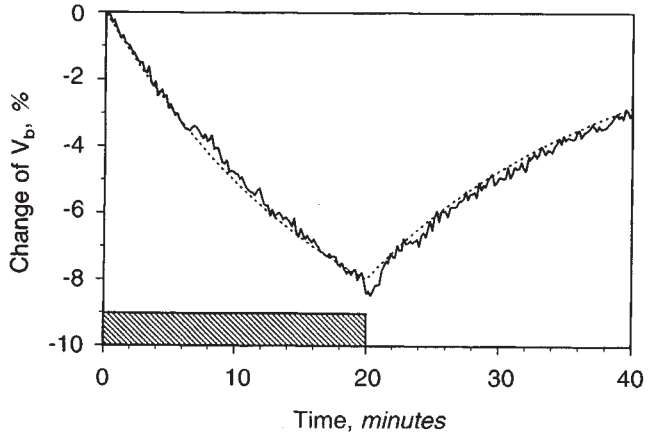

Fig. 4. *Dynamics of V_b.* The relative change of V_b during ultrafiltration (indicated by the bar) and in the subsequent refilling phase was calculated from on-line ultrasonic measurement (full line according to [14]) and from the kinetic model (broken line). (HaMa, J_{UF} = −43.8 ml/min, dry weight = 55.5 kg, whole body Hct = 23.1%, c_p = 67.1 g/liter, $V_{b,calc}$ = 4.6 liter). The parameters for the kinetic model fit were: $L_{p,fit}$ = 7.2 ml/(min · mm Hg · 50 kg LBM) and $V_{b,fit}$ = 6.7 liter.

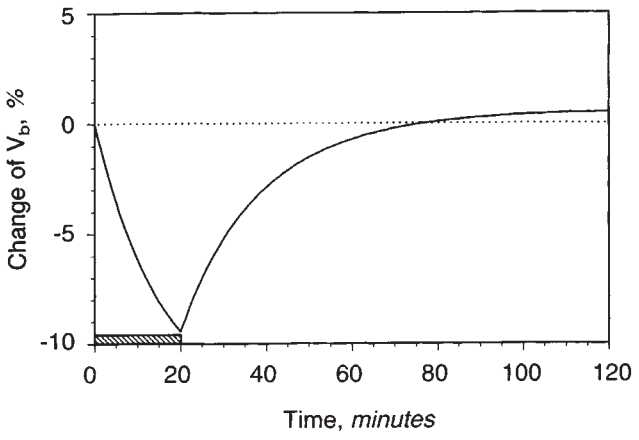

Fig. 5. *Dynamics of V_b.* Mean relative change of blood volume for all studies was calculated from the model and extrapolated to 120 minutes. The ultrafiltration phase is indicated by the bar. Except for starting V_b which was assumed to be increased by 30%, initial values were taken from results (Tables 1 to 4). Notice the estimated increase of V_b at the end of the extrapolation.

lymph flow and/or lymph protein concentration would have to increase considerably.

The increase of intravascular protein mass is a well known phenomenon following hemorrhage in the experimental animal [20, 21]. Zollinger [22] observed that protein refilling via left thoracic duct lymph, following a rapid but subacute hemorrhage of −15%, decreased rather than increased, and concluded that the increase of intravascular protein mass resulted from reduced outward filtration of protein in the microvasculature.

While the volume loss was similar to this study, its nature and its rate was different. This difference is very significant. With hemorrhage the volume loss was iso-oncotic, and considering Starling's hypothesis, only a change in hydrostatic pressure gradients could have induced vascular refilling. However, with ultrafiltration the resulting increase of plasma colloid-osmotic pressure itself facilitated vascular refilling from extravascular spaces. Therefore, when compared to hemorrhage, the driving forces produced by ultrafiltration were much more pronounced.

Since an increase of protein backflow via lymph is unlikely, we tend to follow the hypothesis given by Moore [21] and claim that excess protein refilling occurs in the microvasculature by backfiltration. As long as the exact mechanism of this transport is not clarified we further assume that the transport is effectuated passively by solvent-drag.

Assumption of c_{ref} in the range of 7 g/liter partly corresponds to conclusions drawn from previous investigations. Assuming

an interstitial protein concentration of 20 g/liter, we estimate a protein reflection coefficient of 0.65 for high refilling flows. This assumption is consistent with reported albumin extravasation rates and albumin reflection coefficients [19] found with filtration, that is, flow in the opposite direction. But the low estimate for c_{ref} in refilling volume contrasts with previous results obtained by the same technique and similar analysis [5] which is probably due to a different relation between ρ_p and c_p for uremic plasma samples (Fig. 3). In support of this, the relation presented here compares well to data obtained from the plasma of uremic children [23]. When compared with data from the literature, measured plasma density values are increased relative to values which are calculated from plasma protein concentration [16]. The deviation of plasma density in uremic plasma may be explained by a greater fraction of non-protein components such as urea, by a different protein composition and, possibly, by uremia-induced changes in protein structure [24].

Filtration coefficient

According to Starling's hypothesis, fluid shifts between the capillaries and the interstitium are determined by the sum of colloid-osmotic and hydrostatic pressure gradients and by the filtration coefficient of the capillary wall. These properties are not the same throughout the microvascular system, and the filtration coefficient varies considerably from one tissue to the other. The whole body filtration coefficient represents a mean value of the filtration coefficients of all segments of the microvasculature, each segment weighted for its fraction in capillary surface area. A change in blood flow distribution to different sections of the microvasculature will therefore influence the whole body filtration coefficient. On the other hand, a registered change in the mean filtration coefficient may be useful and indicate a change in the pattern of blood flow distribution. To determine the filtration coefficient, it is practical to consider accessible parameters and to assume (or to assure) that other parameters remain unchanged within the observation period. The shorter the observation period the more likely is it that this assumption applies. With on-line and non-invasive monitoring of blood volume changes this approach may now utilize a practical tool.

To reduce the influence of changes in tissue hydration and microvascular perfusion the experiment was made within a short period of time and it was made at the beginning of the treatment with the patient in a state of pronounced overhydration. The volume ultrafiltrated during the experimental phase was small and corrected for the estimated degree of fluid overload. This was different from the protocol of a related investigation where ultrafiltration volume was the same for different patients and independent of body weight, and where a clear influence of interstitial fluid volume on vascular refilling was observed [8]. While ultrafiltration rate was high for a 20 minutes interval (-35 ± 12 ml/min), only 20% of the volume ultrafiltrated during the whole hemodialysis treatment was removed during the experimental period.

The filtration coefficient in the range of 5.6 ml/(min · mm Hg · 50 kg LBM) compares well to data reported previously [18, 25, 26]. It is in the same range as the one for skeletal muscle (0.01 ml/(min · mm Hg 100 g) [27].

The patients in this study were not representative of the dialysis population as they were known to be cardiovascularly stable during hemodialysis treatments. Thus, the risk of hypotension and its interference with the experiment was minimized. This might be the reason for the small range of filtration coefficients found in this group. While no obvious reason and no clinical correlate could be found for the low filtration coefficients, two patients with the highest filtration coefficients (HaMa, ScJo) were apparently overhydrated, one with edema of the lower limb and one with congestive heart failure. In these cases it was also observed that fluid deliberately entered the vascular compartment even during the initial equilibration phase without ultrafiltration—most probably a result of the change in body position—and that blood volume initially increased by as much as +5%. Typical volume shifts following positional changes [28] without ultrafiltration equilibrated within the pre-experimental period. The prolonged equilibration in these patients suggests that considerable fluid volume may have accumulated in the lower parts of the body. In contrast, the equilibration phases of the patients with low filtration coefficients (HeSo, WoAn, LeTe) showed almost no blood volume increase.

Dynamics of blood and plasma volume

The dynamics of blood volume during ultrafiltration and vascular refilling were described in a model where two model parameters, the initial blood volume ($V_{b,fit}$), and the filtration coefficient ($L_{p,fit}$) were determined from fitting the model to experimental data. Other parameters such as hematocrits and plasma protein concentrations were obtained from the blood sample taken at the beginning of ultrafiltration (Tables 2 and 3, sample 'before ultrafiltration'). Comparison of the fitted blood volume ($V_{b,fit}$) to the blood volume calculated from anthropometric data ($V_{b,calc}$) showed an average relative excess of fitted blood volume by +21%. This difference is plausible, patients being volume loaded at the beginning of ultrafiltration treatment. Interestingly, this difference is much smaller in the patients with very low filtration coefficients (HeSo, GaGi; Table 4). The significant positive correlation between filtration coefficient and estimated blood volume excess ($\Delta Vb/V_{b,calc}$) shows that vascular refilling is enhanced in states of overhydration when compared to states of normal hydration. This relation has previously been described in related terms: the blood volume drop per unit of ultrafiltration exponentially decreased with increased overhydration [29].

The kinetic model describes overshooting plasma and blood volume recovery following ultrafiltration. This effect is essentially due to the protein backflow (J_{Prot}) and to the increase of intravascular protein mass (**Appendix C**, Eq. C7). Therefore, a volume larger than that withdrawn by ultrafiltration has to be refilled in order to attain colloid-osmotic equilibrium. Referring to average data of this investigation, colloid-osmotic equilibrium was not attained within the 20 minutes of the recovery phase. Therefore, the clear overshoot in vascular refilling is not readily seen at the end of the experimental period. However, extrapolation of modeled blood volume changes to two hours shows the theoretical overshoot. This estimate is significant because both an increase of intravascular protein mass and an overshoot of plasma volume following ultrafiltration have been occasionally observed [8, 30]. Paradoxical at first sight, the observation that blood volume may increase with ultrafiltration

was often dismissed as hardly explainable. We now believe that this effect is produced by the low but definite protein content in the refilling volume.

Summary

The composition and the rate of vascular refilling from the extravascular compartment was studied during the early phase of hemodialysis and ultrafiltration treatments. The investigation utilized a continuous and non-invasive blood volume monitoring technique. Refilling volume was calculated to contain a small but definite amount of protein which accounted for the increase of intravascular protein mass following ultrafiltration and which may produce an occasional net overshoot in blood and plasma volume recovery. Refilling rates were characterized by filtration coefficients which corrected for individual differences in ultrafiltration rates, blood volumes, hematocrits and plasma protein concentrations (plasma colloid-osmotic pressures).

The dynamics of blood and plasma volume during ultrafiltration were analyzed by fitting a model to on-line registrations of blood volume changes. Two parameters, the initial blood volume and the filtration coefficient, were obtained from these fits. Fitted blood volume was generally increased when compared to the estimate derived from patient lean body mass. Both parameters may be useful for the prescription of ultrafiltration treatment. The blood volume may be used to estimate the volume overload while the filtration coefficient may be used to determine the rate at which the excess volume can be removed. With techniques which permit analyzing the response of blood volume to ultrafiltration within a short period of time—where experimental conditions may well be controlled—it should be possible to prescribe adequate ultrafiltration for subsequent treatment phases or even for the whole remaining treatment session. However, this remains to be investigated in future studies.

Acknowledgments

This work was supported by the Austrian National Science Fund (project # J-0581). Part of this work has been presented at the XXVIIth Congress of the European Dialysis and Transplantation Association in Vienna, September 1990 and at the 24th Annual Meeting of the American Society of Nephrology in Baltimore, November 1991.

Reprint requests to Daniel Schneditz, Ph.D., Department of Physiology, Karl-Franzens University Graz, Harrachgasse 21/5, 8010 Graz, Austria.

Appendix A. Density of refilling volume

During the recovery phase refilling volume (index ref) is added to the blood. The volume (V) balances for plasma (index p) and blood (index b), where indices 1 and 2 refer to the beginning and to the end of the recovery phase, are given by

$$V_{p2} = V_{p1} + V_{ref} \quad \text{(Eq. A1)}$$

$$V_{b2} = V_{b1} + V_{ref}. \quad \text{(Eq. A2)}$$

Similarly, the mass balances, where ρ is the fluid density, are given by

$$\rho_{p2} \times V_{p2} = \rho_{p1} \times V_{p1} + \rho_{ref} \times V_{ref} \quad \text{(Eq. A3)}$$

$$\rho_{b2} \times V_{b2} = \rho_{b1} \times V_{b1} + \rho_{ref} \times V_{ref}. \quad \text{(Eq. A4)}$$

with

$$V_{p1} = (1 - Hct_1) \times V_{b1} \quad \text{(Eq. A5)}$$

which relates initial plasma volume to initial blood volume by hematocrit (Hct), and with substitution for V_{p2} and V_{b2}, (Eq. A3) and (Eq. A4) are transformed into

$$(\rho_{ref} - \rho_{p2}) \times V_{ref} = (\rho_{p2} - \rho_{p1}) \times V_{b1} \times (1 - Hct_1) \quad \text{(Eq. A6)}$$

$$(\rho_{ref} - \rho_{b2}) \times V_{ref} = (\rho_{b2} - \rho_{b1}) \times V_{b1}. \quad \text{(Eq. A7)}$$

Elimination of V_{ref}/V_{b1} yields

$$\frac{\rho_{b2} - \rho_{b1}}{\rho_{ref} - \rho_{b2}} = \frac{(1 - Hct_1) \times (\rho_{p2} - \rho_{p1})}{\rho_{ref} - \rho_{p2}} \quad \text{(Eq. A8)}$$

which can be rearranged to give an expression for ρ_{ref}

$$\rho_{ref} = \frac{\Delta\rho_b \times \rho_{p2} - \Delta\rho_p \times \rho_{b2} \times (1 - Hct_1)}{\Delta\rho_b - \Delta\rho_p \times (1 - Hct_1)} \quad \text{(Eq. A9)}$$

where $\Delta\rho_b$ is $(\rho_{b2} - \rho_{b1})$ and where $\Delta\rho_p$ is $(\rho_{p2} - \rho_{p1})$.

Appendix B. Relative blood volume changes

For a phase of ultrafiltration and vascular refilling, the volume (V) and mass (m) balances for plasma (index p) and blood (index b) can be written as:

$$V_{p2} - V_{p1} = V_{b2} - V_{b1} \quad \text{(Eq. B1)}$$

and

$$\rho_{p2} \times V_{p2} - \rho_{p1} \times V_{p1} = \rho_{b2} \times V_{b2} - \rho_{b1} \times V_{b1}, \quad \text{(Eq. B2)}$$

where ρ is the density and where the indices 1 and 2 refer to the beginning and to the end of the experimental phase, respectively.

Initial plasma volume is related to initial blood volume by hematocrit

$$V_{p1} = (1 - Hct_1) \times V_{b1}. \quad \text{(Eq. B3)}$$

Plasma volume at the end of the experimental period is obtained from inserting (Eq. B3) into (Eq. B1)

$$V_{p2} = V_{b2} - V_{b1} + (1 - Hct_1) \times V_{b1}. \quad \text{(Eq. B4)}$$

Substitution of V_{p1} and V_{p2} in (Eq. B2) yields

$$\rho_{b2} \times V_{b2} - \rho_{b1} \times V_{b1} = \rho_{p2} \times (V_{b2} - V_{b1}) + (\rho_{p2} - \rho_{p1}) \times V_{b1} \times (1 - Hct_1). \quad \text{(Eq. B5)}$$

With

$$\Delta V = V_{b2} - V_{b1} \quad \text{(Eq. B6)}$$

and with (Eq. B5) an expression for the change of blood volume relative to initial blood volume is then obtained

$$\frac{\Delta V}{V_{b1}} = \frac{V_{b2} - V_{b1}}{V_{b1}} = \frac{\Delta\rho_p \times (1 - Hct_1) - \Delta\rho_b}{\rho_{b2} - \rho_{p2}}, \quad \text{(Eq. B7)}$$

where $\Delta\rho_b$ is $(\rho_{b2} - \rho_{b1})$ and where $\Delta\rho_p$ is $(\rho_{p2} - \rho_{p1})$.

Appendix C. Dynamics of plasma volume (V_p) during ultrafiltration and vascular refilling

Let

$$\frac{dV_p}{dt} = J_{UF} + J_{REF}, \quad \text{(Eq. C1)}$$

where J_{UF} is the ultrafiltration flow and J_{REF} is the refilling flow (Fig. 1). Flow into the vascular system such as refilling flow has a positive and flow out of the vascular system such as ultrafiltration flow has a negative notation. According to Starling's hypothesis, J_{REF} is proportional to the filtration coefficient (L_p), to the colloid-osmotic pressure

gradient ($\Delta\pi = \pi_p - \pi_i$) as well as to the mean hydrostatic pressure gradient (Δp) between the plasma and the interstitium:

$$J_{REF} = L_p \times (\Delta\pi - \Delta p) \quad \text{(Eq. C2)}$$

Colloid osmotic pressure is related to protein concentration [18] so that

$$\pi_p = a_1 \times c_p + a_2 \times c_p^2 + a_3 \times c_p^3 \quad \text{(Eq. C3)}$$

$$\pi_i = a_1 \times c_i + a_2 \times c_i^2 + a_3 \times c_i^3, \quad \text{(Eq. C4)}$$

where c_p stands for plasma protein concentration and c_i for interstitial protein concentration. With Eq. C2 to C4, Eq. C1 may be transformed into

$$\frac{dV_p}{dt} = J_{UF} + L_p \times \{[a_1 \times (c_p - c_i) + a_2 \times (c_p^2 - c_i^2) + a_3 \times (c_p^3 - c_i^3] - \Delta p\}. \quad \text{(Eq. C5)}$$

Both c_p and intravascular protein mass ($m_p = V_p \times c_p$) are functions of time. Therefore

$$\frac{dc_p}{dt} = \frac{d\left(\frac{m_p}{V_p}\right)}{dt} = \frac{\left(\frac{dm_p}{dt}\right)V_p - \left(\frac{dV_p}{dt}\right)m_p}{V_p^2}. \quad \text{(Eq. C6)}$$

Since

$$\frac{dm_p}{dt} = J_{Prot} = J_{REF} \times c_{ref} = \left(\frac{dV_p}{dt} - J_{UFR}\right) \times c_{ref}, \quad \text{(Eq. C7)}$$

where J_{Prot} is the protein flow, Eq. C6 can be transformed into

$$\frac{dc_p}{dt} = \frac{\left(\frac{dV_p}{dt}\right) \times (c_{ref} - c_p) - J_{UF} \times c_{ref}}{V_p} \quad \text{(Eq. C8)}$$

The change of interstitial (V_i) and of interstitial protein mass (m_i) is determined by refilling flow (J_{REF}) and by protein flow (J_{Prot})

$$\frac{dV_i}{dt} = -J_{REF} = J_{UF} - \frac{dV_p}{dt} \quad \text{(Eq. C9)}$$

$$\frac{dm_i}{dt} = -J_{Prot} = -J_{REF} \times c_{ref} = \frac{dV_i}{dt} \times c_{ref}, \quad \text{(Eq. C10)}$$

so that the change of interstitial protein concentration (c_i)

$$\frac{dc_i}{dt} = \frac{d\left(\frac{m_i}{V_i}\right)}{dt} = \frac{\left(\frac{dm_i}{dt}\right) \times V_i - \left(\frac{dV_i}{dt}\right) \times m_i}{V_i^2} \quad \text{(Eq. C11)}$$

can be rewritten as

$$\frac{dc_i}{dt} = \frac{\left(\frac{dV_i}{dt}\right) \times (c_{ref} - c_i)}{V_i}. \quad \text{(Eq. C12)}$$

The system of differential equations (Eqs. C5, C8, C9 and C12) was solved for V_p by numerical integration according to Runge-Kutta [31].

References

1. Daugirdas JT: Dialysis hypotension: A hemodynamic analysis. *Kidney Int* 39:233–246, 1991
2. Hainsworth R: The importance of vascular capacitance in cardiovascular control. *News Physiol Sci* 5:250–254, 1990
3. Sherman RA: The pathophysiologic basis for hemodialysis-related hypotension. *Semin Dial* 1:136–142, 1988
4. Kenner T, Moser M, Hinghofer-Szalkay H: Determination of cardiac output and transcapillary fluid exchange by continuous recording of blood density. *Basic Res Cardiol* 75:501–509, 1980
5. Hinghofer-Szalkay H: Continuous blood densitometry: Fluid shifts after graded hemorrhage in animals. *Am J Physiol* 250:H342–H350, 1986
6. Wraight EP: Capillary permeability to protein as a factor in the control of blood volume. *J Physiol* 237:39–47, 1974
7. Hinghofer-Szalkay H, Moser M: Fluid and protein shifts after postural changes in humans. *Am J Physiol* 250:H68–H75, 1986
8. Koomans HA, Geers AB, Dorhout Mees EJ: Plasma volume recovery after ultrafiltration in patients with chronic renal failure. *Kidney Int* 26:848–854, 1984
9. Joles JA, Kortlandt W, de Mik H, Koomans HA: Effect of hypoproteinemia on blood volume recovery after moderate hemorrhage in conscious splenectomized dogs. *J Surg Res* 47:515–519, 1989
10. Bauer JH, Brooks CS: Body fluid composition in chronic renal failure. *Clin Nephrol* 16:114–118, 1981
11. Kenner T: The measurement of blood density and its meaning. *Basic Res Cardiol* 84:111–124, 1989
12. Schneditz D, Heimel H, Stabinger H: Sound speed, density and total protein concentration of blood. *J Clin Chem Clin Biochem* 5:803–806, 1989
13. Schneditz D, Pogglitsch H, Horina J, Binswanger U: A blood protein monitor for the continuous measurement of blood volume changes during hemodialysis. *Kidney Int* 38:342–346, 1990
14. Moser M, Vauti F, Pinter H, Kenner T: Circadian variation of volume and concentration of orthostatically shifted fluid. *The Physiologist* 28:317–318, 1985
15. Boer P: Estimated lean body mass as an index for normalization of body fluid volumes in humans. *Am J Physiol* 247:F632–F636, 1984
16. Holzer H, Leopold H, Hinghofer-Szalkay H, Stuebchen-Kirchner H, Maurer E: Determination of the serum protein concentration based on the measurement of density by the mechanical oscillator technique. *J Clin Chem Clin Biochem* 16:391–395, 1978
17. Schneditz D, Roob J, Haas G, Moser M, Pogglitsch H, Kenner T, Binswanger U: The nature of transvascular fluid shifts during ultrafiltration treatment. (abstract) *Kidney Int* 39:1329, 1991
18. Landis EM, Pappenheimer JR: Exchange of substances through the capillary walls, in *Handbook of Physiology, Section 2, Circulation* (vol II), edited by Hamilton WF, Dow P, Washington, D.C., Am Physiol Soc, 1963, pp. 961–1034
19. Taylor AE, Granger DN: Exchange of macromolecules across the microcirculation, in *Handbook of Physiology, Section 2, Cardiovascular System* (vol IV, part 1), edited by Renkin ME, Michel CC, Geiger SR, Bethesda, MD, Am Physiol Society, 1984, p. 467–520
20. Skillman JJ, Eltringham WK, Goldensen RH, Moore F: Transcapillary refilling after hemorrhage in the splenectomized dog. *J Surg Res* 8:57–67, 1968
21. Moore F: The effects of hemorrhage on body composition. *N Engl J Med* 273:567–577, 1965
22. Zollinger RM Jr: Plasma volume and protein restoration after hemorrhage: Role of the left thoracic duct versus transcapillary refilling. *J Surg Res* 12:151–160, 1972
23. Pardemann G, Genzow K, Lerche D, Paulitschke M: Präzisionsmessungen der Dichte von Blut und Blutplasma. *Zeitschrift für medizinische Labordiagnostik* (in press)
24. Durchschlag H, Jaenicke R: Partial specific volume changes of proteins; densimetric studies. *Biochem Biophys Res Commun* 108:1074–1079, 1982
25. Keshaviah PR, Ilstrup KM, Shapiro FL: Dynamics of vascular refilling, in *Progress in Artificial Organs-1983*, edited by Atsumi K, Maekawa M, Ota K, Cleveland, ISAO Press, 1984, pp. 506–511
26. Isogai Y, Nose H, Miki K, Morimoto T: Dynamics of fluid movement between intravascular and interstitial spaces. *J Theor Biol* 100:305–317, 1983
27. Michel CC: Fluid movements through capillary walls, in *Handbook of Physiology, Section 2, Cardiovascular System* (vol IV, part

1), edited by RENKIN ME, MICHEL CC, GEIGER SR, Bethesda, MD, Am Physiol Society, 1984, pp. 375–409
28. HINGHOFER-SZALKAY H, MOSER M: Fluid and protein shifts after postural changes in humans. *Am J Physiol* 250:H68–H75, 1986
29. MANN H, STILLER S, SCHALLENBERG U, THÖMMES A: Optimizing dialysis by variation of ultrafiltration-rate and sodium concentration controlled by continuous measurement of circulating blood volume, in *Contributions to Nephrology, Improvements in Dialysis Therapy* (vol. 74), edited by BALDAMUS CA, MION C, SHALDON S, Basel, S. Karger, 1989, pp. 182–190
30. GOLIA T, BINSWANGER U: Blood volume changes during short dialysis. (abstract) *XXVIth Congress European Renal Association*, Göteborg, 1989, p. 164
31. EBERT K, EDERER H, ISENHOUR TL: *Computer Applications in Chemistry. An Introduction for PC Users*. New York, VCH Publishers, 1989, pp. 290–298