The Relationship Between Systemic and Whole-Body Hematocrit Is Not Constant during Ultrafiltration on Hemodialysis

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Abstract. The measurement of relative blood volume (RBV) changes during ultrafiltration assume a constant mass and distribution of circulating blood components such as hematocrit. The authors examine the validity of this assumption in 10 subjects undergoing repeated direct measurements of systemic hematocrit and plasma volume (PV_{icg}) using indocyanine green dilution at four stages of dialysis with intermittent ultrafiltration. Ultrasonic RBV changes were monitored. Absolute blood volumes (ABV) were initially derived for each PV_{icg} estimate, and corresponding measured systemic hematocrit was adjusted by a factor of 0.86 to correct for the difference between the systemic and whole-body hematocrit (constant Fcell ratio). PV_{icg} and ABV changes correlated closely ($R = 0.98$; $P < 0.001$). ABV changes overestimated reduction in PV_{icg} during ultrafiltration (mean difference, -140 ± 202 ml). The calculated red cell mass however was variable ($P < 0.01$). Fcell ratio was then adjusted at each blood volume measurement ($Fcell_1$, 0.87 ± 0.02; $Fcell_2$, 0.89 ± 0.03; $Fcell_3$, 0.94 ± 0.06; $Fcell_4$, 0.94 ± 0.04; $P < 0.01$) to maintain a constant red cell mass (2146 ± 460 ml). When ABV was recalculated using PV_{icg}, systemic hematocrit and variable Fcell ($ABV_{Fvariable}$), the mean difference between PV_{icg} changes and $ABV_{Fvariable}$ changes, was negligible (-0.2 ± 35 ml). During intermittent ultrafiltration, RBV changes systematically underestimated the percentage reduction in ABV (mean difference, $7.7 \pm 10.6\%$). When corrected for variations in Fcell, $ABV_{Fvariable}$ and RBV differences were negligible (mean difference $1.2 \pm 2.6\%$). Varying Fcell ratio probably reflects microvascular volume change with net fluid shift from the microcirculation to macrocirculation (intravascular refill). This may result in underestimation of changes in systemic hematocrit and RBV during dialysis such that they were less than those predicted by directly measured changes in plasma volume.

Technological advances have allowed the development of devices that can continuously and noninvasively monitor biologic constituents (hematocrit [Hct] and plasma protein concentration) during hemodialysis (HD) treatment. Hct and relative blood density changes online during HD have been advocated as tools for assessing blood volume (BV) changes induced by ultrafiltration (UF) (1). The assumptions that changes in the measured systemic Hct (Hct_{sys}) result solely from circulating plasma volume (PV) changes induced by UF and that there is uniform mixing of a constant circulating mass of red cells and plasma components in the whole circulation during UF form the basis of such indirect measurements.

Attempts to quantify volume shifts precisely in the vascular compartment using relative changes have been difficult as they often underestimate directly measured BV changes (2). Apparent relative BV (RBV) changes therefore cannot be explained by PV depletion alone. Observational studies to analyze the RBV traces or determine the critical Hct for hypotension suggest wide

degrees of interpatient and intrapatient variability during HD with UF (3). These suggest that other physiologic mechanisms and alterations that affect distribution of the circulatory components during UF may influence these indirect estimates (2).

Accurate measurements of red cell volume by radioactive isotopes show that the relative volumes of red cells and plasma in the circulation as a whole (whole-body hematocrit [Hct_w]) differ from those found in the venous blood (Hct_{sys}). The difference between the systemic hematocrit in the Hct_{sys} and Hct_w is expressed as the Fcell ratio (Hct_w/Hct_{sys}). In the steady state, this is due to a dynamic reduction in microvascular Hct during blood flow through the capillaries and venules (<200 μm). This is also known as the Fahraeus effect (4) and depends on the capacity of the microcirculation. Reduction is greater in smaller vessels as a result of anomalous flow properties of blood (5). The use of changes in Hct_{sys} to reflect BV changes accurately depends on the constancy of the relationship of Hct_w to Hct_{sys} during UF. To our knowledge, the assumption of constancy of Fcell ratio during dialysis with UF has not been investigated. This study examines the validity of this assumption and hypothesizes that there are significant changes in the microcirculation during UF that affect Hct redistribution and RBV changes.

Materials and Methods

Subjects

We studied 10 subjects (eight male) using repeated measurements of PV and Hct during a single supine HD session with intermittent UF

(3 L/hr). Four intermittent UF pulses were used removing successively 40–20–20–20% of total UF volume between intervening rest periods. Subjects had received chronic HD for at least 6 mo and had a stable dry weight. The presence of iodine allergy, eosinophilia, abnormal liver function tests, raised serum IgE levels, or significant access recirculation within 1 mo before the study was an exclusion criterion. The North Herts Ethical Review committee approved the study. All patients gave informed consent. All were treated with thrice-weekly high-flux bicarbonate HD (Fresenius 4008E) using polyamide membranes and AV fistulae. Blood flow rates were in the range of 350 to 450 ml/min, and the mean sessional Kt/V was 1.24 $\pm$ 0.16 (6).
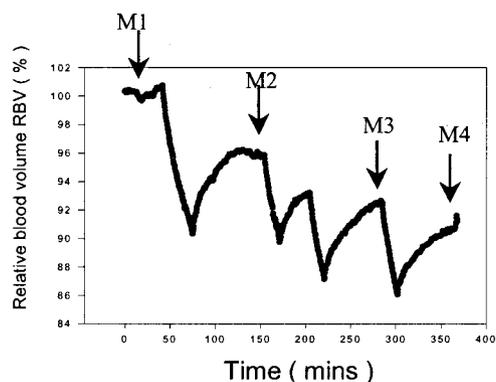
PV Measurement

PV was measured by dye dilution using indocyanine green (7). Four estimates of PV (i = 1 to 4) were obtained during a single HD session in each patient. All measurements were made in stable supine position. UF was commenced after an equilibration period of 20 min from the connection to the extracorporeal circuit. PV measurements were made before the start and at the end of the first and fourth UF pulses (Figure 1) when steady-state BV conditions were obtained on the RBV monitor (RBV plateau with variations of <0.5% over at least a 10-min period).

Tracer

The tracer used was Cardiogreen (ICG Green Sterile indocyanine green USP Fluka), a tricarbocyanine dye, molecular weight 775, with an absorption peak at 805 nm. The dye is nontoxic, confined to plasma, not subject to extravascular distribution, and not metabolized or degraded. After equilibration, the dye decays fast in an exponential manner. It is exclusively taken up by the liver and has a plasma half-life of 2 to 3 min (8).

Procedure for Determination of PV

Before each dye injection, blood was withdrawn for Hct and baseline plasma blank in heparinized syringes. ICG (25 mg) was dissolved in 10 ml of sterile aqueous solvent to produce ICG solution

Blood volume changes during Stepwise Ultrafiltration M1-M4 plasma volume (ICG) measurements

Figure 1. Relative blood volume (RBV) profile during intermittent ultrafiltration (UF) in a subject on hemodialysis (HD). Arrows indicate the timing of the four steady-state hematocrit (Hct) and direct plasma volume (ICG) measurements. M1, measurement before onset of UF; M2, after 40% UF; M3, after 80% UF; M4, after 100% UF removed.

of 2.5 mg/ml. The dye (10 mg) was then injected as rapidly as possible into a venous port beyond the bubble trap. All syringes were weighed on a precision scale before and after the injection to determine the precise quantity injected. Exactly 3 min after the end of the injection, sampling was commenced from the arterial port in heparinized syringes at 1-min intervals for 10 min (eight samples). Samples were centrifuged at 3000 rpm for 10 min. The plasma blank sample was used to determine the baseline background absorption at 805-nm wavelength. The absorption of ICG dye in the timed plasma samples were then compared against the baseline at the same wavelength (8). A five-point calibration was performed for each BV measurement using the blank plasma sample just before dye injection.

Analysis

The natural logarithms of the measured ICG dye concentrations were plotted against time for each PV measurement, and the best-fit linear regression was obtained. The logarithm of the dye concentration at $t = 0$ was obtained by extrapolation. The antilog of this yielded the initial dye concentration in plasma at the time of injection. Plasma volume (PV_{icg}) was calculated according to the following equation

$$Plasma\ volume^{[9]} = \frac{dye\ infused\ (mg)}{plasma\ dye\ concentration\ (mg/l)} \quad (1)$$

Hct Determination

Hct_{sys} was measured using aperture impedance counters (Coulter-STKS) (9). All patients were monitored with relative blood volume (RBV_{BVM}) monitor (1) and oscillometric BP.

Procedure for Determination of Absolute BV and Red Cell Mass

1. Absolute BV ($ABV_{Fconstant}$) (10) estimates were derived for each PV estimate and corresponding measured Hct_{sys} adjusted by a factor of 0.86 to correct for the difference between the Hct_{sys} and Hct_w (constant Fcell ratio):

$$ABV_{Fconstant} = \frac{plasma\ volume}{1 - (Hct_{sys})*Fcell} \quad (2)$$

2. Total red cell mass ($RCM_{Fconstant}$) estimates were then derived from each $ABV_{Fconstant}$ estimate and the corresponding Hct_w using the following relationship:

$$RCM_{Fconstant} = ABV_{Fconstant} \times Hct_w \quad (3)$$

3. Subsequently, separate Fcell ratios ($[Fcell]_i$) were calculated for each of the four plasma volume (PV_i) and corresponding Hct_{sys} ($[Hct_{sys}]_I$) values obtained during each dialysis session. The calculation assumed that (*1*) RCM remained constant throughout the dialysis session and (*2*) that absolute BV and PV changes during UF were effectively identical.
4. ($ABV_{Fvariable})_i$ was then recalculated from Equation 2 using the appropriate PV_i and ($Hct_{sys})_i$ measurements and the corresponding ($Fcell)_i$.
5. The differences in Fcell ratio between the first ($[Fcell]_1$) and subsequent ($[Fcell]_I$) measurements were used to correct the RBV reading (corrected reading designated as RBV_c) obtained from the RBV monitor at the second (RBV_2), third (RBV_3), and fourth (RBV_4) measurements:

$$RBV_{ci} = RBV_i \times \{1 - [(Fcell)_i - (Fcell)_l]\} \quad (4)$$

Where i = 2 to 4

Table 1. Absolute blood volumes derived by using measured plasma volume, hematocrit, and constant Fcell ratio (0.86) in 10 subjects during hemodialysis

Subjects	ABV1	ABV2	ABV3	ABV4
1	8033	7139	6157	5944
2	5195	4625	3598	3977
3	5994	5578	5262	4881
4	4682	4670	3507	3269
5	8248	7450	6905	6717
6	7726	6849	5790	5093
7	7081	6854	5960	5504
8	7283	6791	6633	6392
9	9670	9450	8781	8363
10	6717	6387	6059	6018

ABV, absolute blood volume.

Statistical Analyses

Statistical methods used were Bland Altman (11) analysis required for comparison of methods, *t* test for comparison of means ($P < 0.05$), linear regression, and Pearson correlation tests. Statistical analysis was performed using software package Sigmaplot (version 2.01).

Results

The subjects had a mean age of 61.6 ± 4.8 yr, a mean dry body weight of 83 ± 17 kg, and a body surface area of 2 ± 0.2 m^2. The mean UF volume removed was 2298 ± 845 ml, and there was a net reduction in PV during dialysis of 1218 ± 474 ml. The mean reduction in weight during dialysis was 2.48 ± 0.9 kg.

The derived values for $ABV_{Fconstant}$ from directly measured plasma volumes (PV_{icg}) and HCT (Equation 1) are shown in Table 1. PV changes and BV changes were highly correlated ($R = 0.98$, $P < 0.001$). When the mean red cell mass ($RCM_{Fconstant}$) was calculated using $ABV_{Fconstant}$ and the measured HCT, there were significant differences between the calculated values obtained at each measured PV_i ($P < 0.01$; Figure 2a).

The assumption of a constant circulating RCM during UF is violated unless there is a progressive increase in Fcell ratio. Hence, the Fcell ratios were corrected for each patient ($Fcell_1$, 0.87 ± 0.02; $Fcell_2$, 0.89 ± 0.03; $Fcell_3$, 0.94 ± 0.06; $Fcell_4$, 0.94 ± 0.04; $P < 0.01$ $Fcell_1$ *versus* $Fcell_3$, $P < 0.001$ $Fcell_1$ *versus* $Fcell_4$) assuming a constant circulating RCM ($RCM_{Fvariable}$ mean, 2146 ± 460 ml; NS; Figure 2b). The resulting ABV estimations ($ABV_{Fvariable}$) are depicted in Table 2. The corrected mean absolute BV obtained at the end of UF was 72.2 ml/kg (Table 2, ABV 4). The change in Fcell ratio (Figure 3) correlated with the UF volume removed ($R = 0.32$, $P < 0.05$).

$ABV_{Fconstant}$ systematically overestimated PV_{icg} with a mean difference of -140 ± 202 ml (Bland Altman analysis; Figure 4a). When corrected for Fcell variation, the mean difference of PV and BV changes were negligible (-0.2 ± 35.8 ml; Figure 4b).

Relative BV changes ($RBV_{bvm}\%$) significantly underestimated the percentage reduction of absolute BV ($ABV_{Fconstant}$) between the four measurements (Table 1) with a mean difference ($\pm SD$) of $7.7 \pm 10.6\%$ (Figure 5a). When corrected for varying Fcell ratio, the mean difference between change in corrected RBV (RBV_C; Equation 4) and absolute BV ($ABV_{Fvariable}$; Table 2) was only $1.2 \pm 2.6\%$ (Figure 5b).

Discussion

The assessment of volume shift using systemic Hct or plasma density is based on mass conservation. The first assumption of a constant total circulating RCM during a dialysis session is true in the absence of hemolysis or blood leak. This parameter is likely to fluctuate over time only with changes in erythropoietin treatment. Red cell volume may vary with
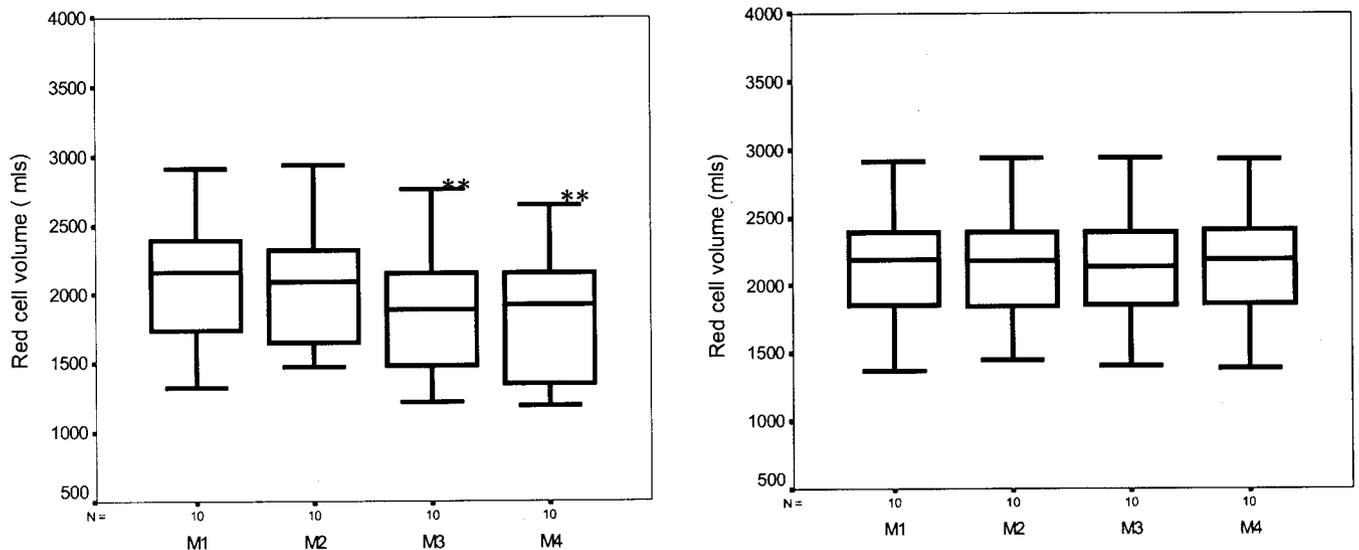

Figure 2. (a) Box plot showing inconstant total red cell volume ($RCM_{Fconstant}$) in 10 subjects during dialysis using constant Fcell (**$P < 0.01$) (b) Box plot showing constant red cell volume using variable Fcell ratio ($RCM_{Fvariable}$; NS).

Table 2. ABV derived by using measured plasma volume, hematocrit, and variable Fcell ratio in same 10 subjects during hemodialysis

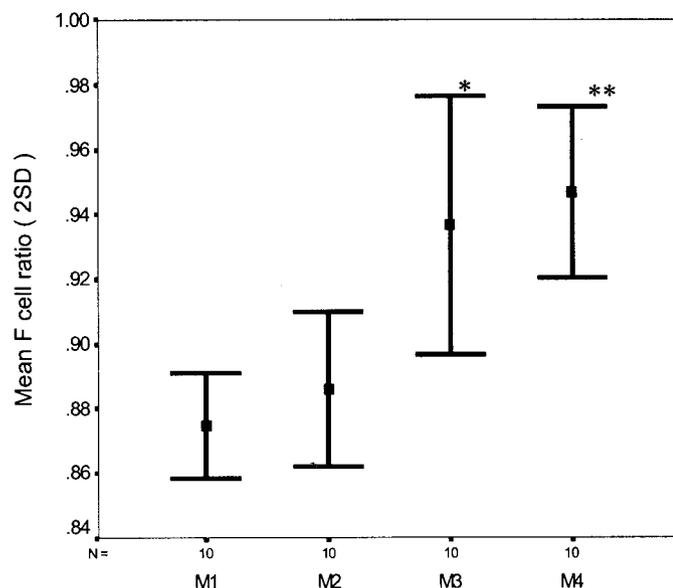| Subjects	ABV1	ABV2	ABV3	ABV4
1	7995	7139	6348	6157
2	5165	4625	3728	4125
3	5964	5578	5455	5074
4	4660	4670	3648	3405
5	8208	7450	7119	6945
6	7701	6849	5928	5220
7	7040	6854	6196	5734
8	7242	6791	6903	6679
9	9621	9450	9062	8642
10	6684	6387	6248	6215

Figure 3. Progressive rise in Fcell ratio obtained in 10 subjects at four steps of intermittent UF (*$P < 0.05$, **$P < 0.01$)

plasma osmolality, but the degree of change is small even across extreme variations in dialysis fluid sodium concentration (12). A second assumption is of constant homogeneous distribution of these components between the macro- and the microcirculation (4) throughout dialysis. The relationship between systemic and whole-body Hct expressed as Fcell ratio is due to microcirculatory effects and remains constant in steady state. This study demonstrates that both of the assumptions cannot be true at the same time during dialysis with UF. The assumption of a constant circulating RCM during UF is violated unless there is a progressive increase in Fcell ratio during UF.

A model of circulatory changes during UF with or without microvascular changes can be hypothesized on the basis of these results (Figure 6). In the steady state (Figure 6a), the intravascular volume (Vb) can be divided into two compartments with proportional distribution of plasma and red cells: the macrocirculation ($V_{mac} = 60\%$; $H_{sys} = 0.35$) and the microcirculation ($V_{mic} = 40\%$; $H_{mic} = 0.233$). If UF were associated with no change in Fcell ratio, then a proportional volume change would occur in each compartment and the observed rise in Hct_{sys} would purely reflect the volume removed from the macrocirculation (Figure 6b). However, the observed underestimation of rise in Hct_{sys} suggests that there are additional physiologic factors in operation. There are two main possibilities. There could be loss of RCM from the systemic circulation, which seems unlikely, or there could be intravascular refill from the micro- to macrocirculation. The latter mechanism results in a new steady state of the microcirculation and an altered higher Fcell ratio (Figure 6c). It is strongly supported by the almost complete correction of systemic RBV underestimation by use of a varying Fcell ratio.

The ratio of the RCM to PV differs in the veins, capillaries, and various organ beds. Any perturbation provokes a proportional change in microvascular and systemic Hct, which can be represented by the constant $\propto$, the value of which is approximately 0.66 based on studies of different microvascular beds (13, 14). Each microvessel generation could constrict in a heterogeneous manner that can be averaged by using the value $\propto$. Because $\propto$ is fairly constant, any rise in Fcell ratio entails a reduction in V_{mic}/V_b (see Appendix). In the hypothetical example depicted in Figure 6, these relationships predict a reduction in V_{mic}/Vb from 21% (Figure 6b) to 12% (Figure 6c). Such models have been used to describe the microvascular circulation under different pathophysiologic conditions (15).

Observations on the hepatic and pulmonary circulation indicate that changes in microvascular volume lead to transient changes in the Hct or density of blood flowing from these organs (16). If the circulation is subjected to any perturbation, which changes the microvascular volume, then this contributes partially to the measured change in the Hct_{sys}. There is no evidence to suggest significant alterations in capillary permeability characteristics during UF (15, 17). Morphometric data indicate that 40 to 50% of BV resides in the microcirculation. Direct microvascular measurements suggest that during hemorrhage, <200-μm-diameter venules form the major reserve capacity of the circulation. Large volumes may be shifted from the micro- to the macrocirculation, reducing the effect of BV loss.

These findings suggest that microvascular change induced by UF is an important factor influencing the Hct_{sys}. This seems to be accentuated at later stages of UF, when a rise in Hct_{sys} may not occur, despite hypovolemia. This is likely to be due to intravascular refill. Studies using tagged red blood cells have suggested that during hypovolemia caused by UF, mobilization of blood from the splanchnic region occurs as a compensatory mechanism (18).

This study provides evidence of dissociation between indirect RBV measurements and direct BV changes measured by indocyanine green during hemodialysis, most apparent at later stages of dialysis with ultrafiltration. Lower BV estimates obtained using radioisotope methods in subjects before the start of dialysis in a previous study (19) are perhaps due to smaller

Bland Altman analysis of plasma and blood volume changes with constant (4A) or varying (4B) F cell ratio
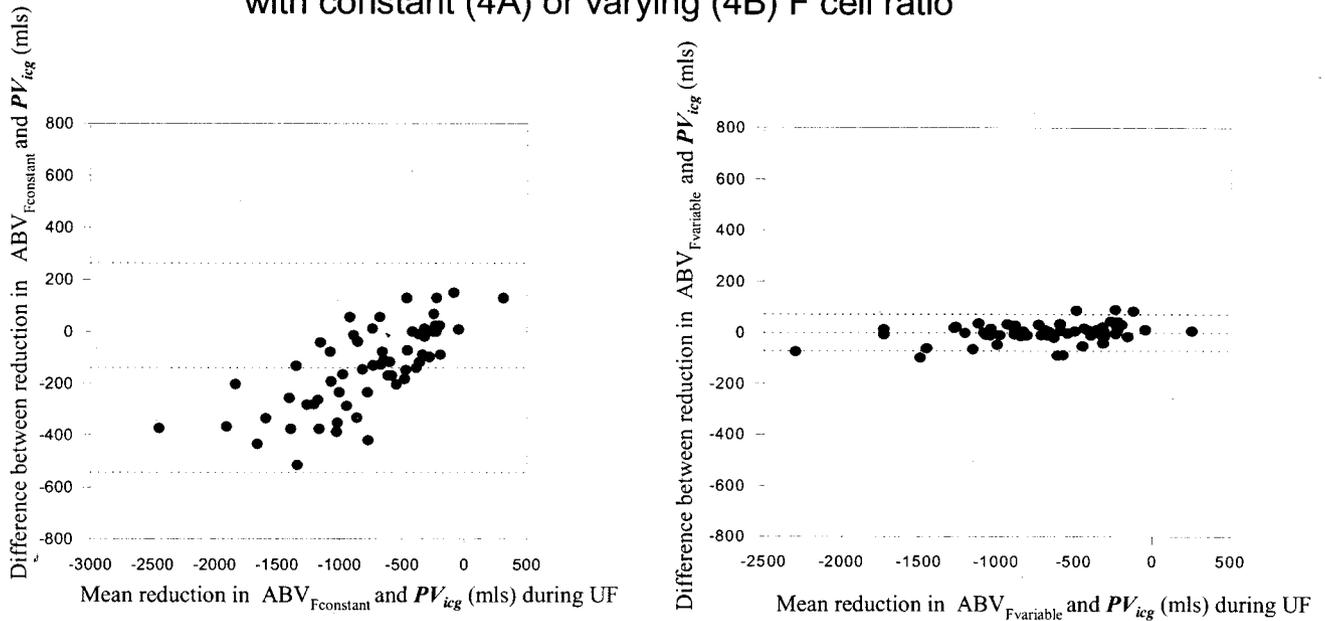

Figure 4. Bland Altman analysis comparing directly measured plasma volume changes and blood volume changes derived using constant Fcell ratio ($ABV_{Fconstant}$; mean difference, -140 ± 202 ml; a) and variable Fcell ratio ($ABV_{Fvariable}$; negligible mean difference, -0.2 ± 35.8 ml; b). Reference lines indicate mean difference $\pm$ 2 SD.

Bland Altman analysis of relative and absolute blood volume changes with constant (5A) or varying (5B) F cell ratio
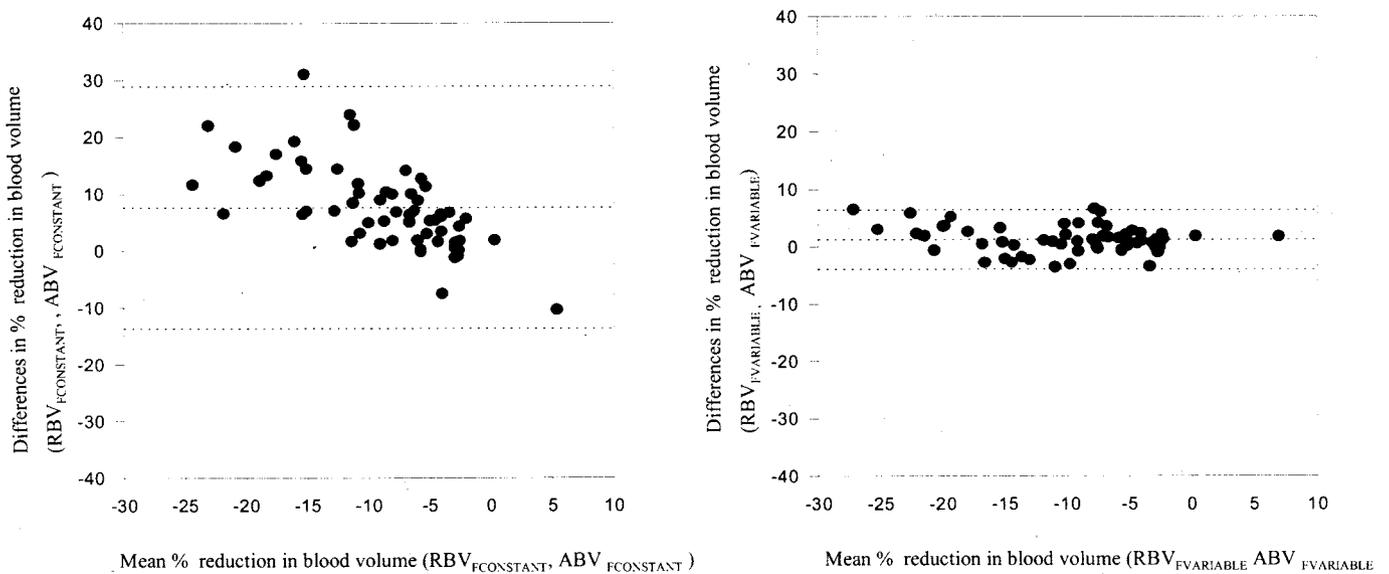

Figure 5. Bland Altman analysis comparing percentage blood volume changes in 10 HD patients during UF as observed by RBV monitor and absolute blood volume measured by ICG technique (% blood volume reduction during UF between all four measurements; $n = 60$). Reference lines indicate mean difference $\pm$ 2 SD. (a) Comparing observed RBV_{BVM} changes and absolute blood volume changes derived from plasma volume, Hct, and Fcell ratio 0.86 ($ABV_{Fconstant}$). (b) Comparing $RBVc_{BVM}$ changes and absolute blood volume changes ($ABV_{Fvariable}$) both corrected for Fcell variation. RBV changes underestimate ABV reduction with constant Fcell assumption by $7.7 \pm 10.6\%$ (a) but by only $1.2 \pm 2.6\%$ when corrected for varying Fcell ratio (b).
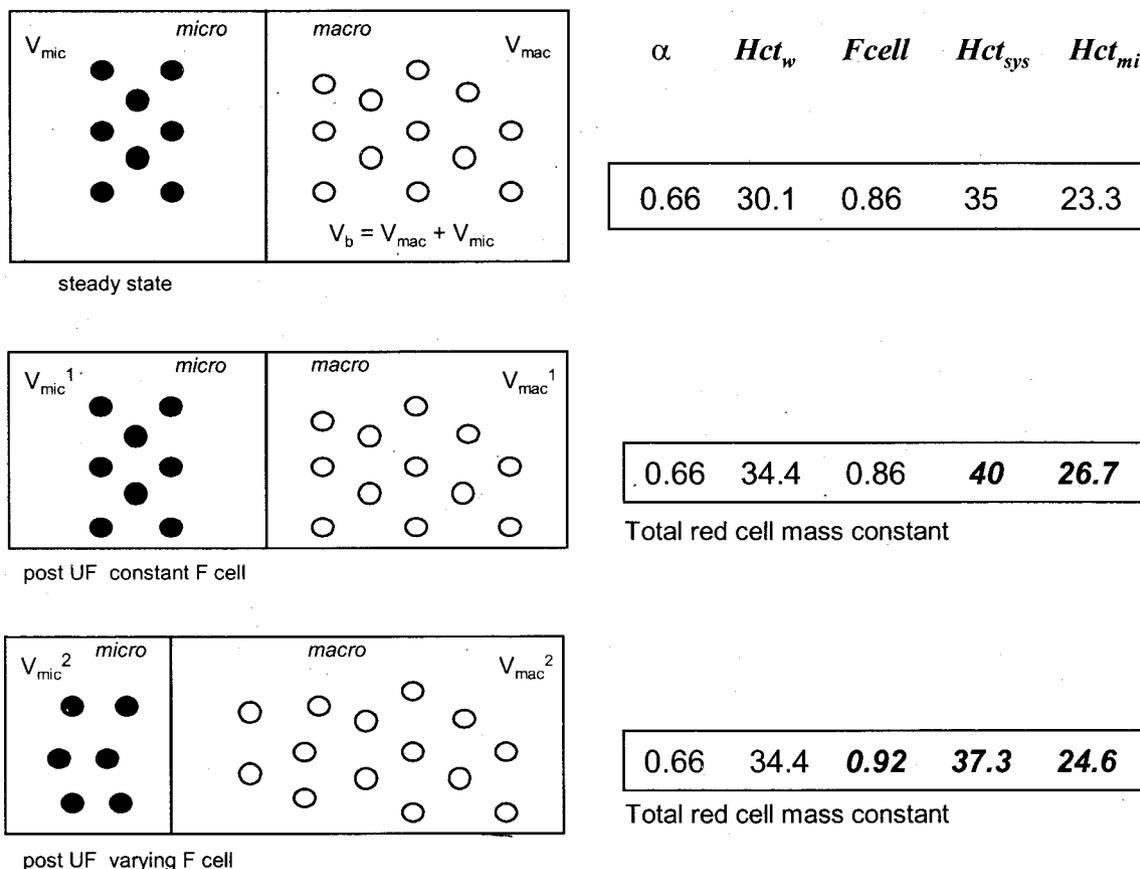
α	Hct_w	$Fcell$	Hct_{sys}	Hct_{mic}
0.66	30.1	0.86	35	23.3

steady state

0.66	34.4	0.86	*40*	*26.7*

Total red cell mass constant

post UF constant F cell

0.66	34.4	*0.92*	*37.3*	*24.6*

Total red cell mass constant

post UF varying F cell

Figure 6. Hypothetical blood volume model demonstrating microvascular volume change. (a) Steady-state control shows uniform systemic hematocrit (Hct_{sys}) for the macrocirculation (right compartment V_{mac}) and the microvascular hematocrit Hct_{mic} for the microcirculation (left compartment V_{mic}) to represent the total red blood cell content in a blood volume Vb and whole-body hematocrit (Hct_w). (b) Post UF considers a state of net volume removed and a static relationship between the contracted macro- (V_{mac}^1) and microcirculation (V_{mic}^1) (constant Fcell). (c) Identical net blood volume depletion with an additional microvascular volume change (V_{mic}^2), resulting in a rise in the Fcell ratio and underestimation of the Hct_{sys} change. It demonstrates a state of redistribution from micro- to macrocirculation (intravascular refill) during UF. $\propto$ (2/3) represents a constant proportional adjustment between the macro- and micro-Hct.

body size, methodologic variations, and differences in hydration status of the subjects studied.

The absolute mass of protein in the vascular space at the time of the dye measurement is not relevant for the PV and BV determination. The dye simply binds instantaneously to the available circulating protein mass. This study assumes that during blood volume steady state with no UF and a relative small sampling period, there is dynamic equilibrium and negligible net flux of protein across capillary membrane. RBV measurements are also based on the same assumption allowing comparison between two methods. Changing vascular refill rates despite apparent steady-state conditions in the RBV profile seem unlikely to account for this, given the degree of underestimation. Although the ultrasonic RBV monitor has a very low noise–signal ratio, momentary fluctuations may introduce potential errors. However, the dissociation is almost eliminated when the variation in Fcell ratio is considered, suggesting that intravascular refill and regional blood flow redistribution during UF significantly affect RBV measurements. These observations and others, such as the RBV changes observed during maximal exercise on dialysis (20), sup-

port the notion that RBV measurements can be significantly affected by procedures that induce changes in the recruitment of the microcirculation.

Conclusion

Microcirculatory changes lead to volume shifts from the micro- to the macrocirculation with adjustment of the macrovascular Hct_{sys} during UF. A compliant microcirculation acts as a blood reservoir allowing volume compensation during UF. Such redistribution leads to a progressive rise in the Fcell ratio during UF in the presence of a constant RCM. Hence, the assumption of a constant and homogeneous Hct distribution during UF is invalid, and the use of Hct_{sys} change as the sole determinant of PV change could be erroneous. Both the blood density and the Hct based equations used to determine changes in RBV ignore volume redistribution between the macro- and microcirculation. This study can serve as the basis to design experiments to characterize the mechanisms that produce microvascular change during UF.

Acknowledgments

Appendix

$$H_{mic}/H_{sys} = H'_{mic}/H'_{sys} = \alpha$$

$$V_{rbc} = (V_b - V_{mic}) \times H_{sys} + V_{mic} \times H_{mic}$$

$$H_w = V_{rbc}/V_b$$

$$= \frac{V_b \times H_{sys} - V_{mic} \times H_{sys} + V_{mic} \times H_{mic}}{V_b}$$

$$= H_{sys} - (H_{sys} - H_{mic})V_{mic}/V_b$$

$$= H_{sys} \times [1 - (1 - H_{mic}/H_{sys})V_{mic}/V_b]$$

$$= H_{sys} \times [1 - \frac{(1-\alpha)V_{mic}]}{V_b}$$

$$F_{CELL} = H_w/H_{sys} = [1 - \frac{(1-\alpha)V_{mic}]}{V_b}$$

where H is hematocrit, V is volumes, b is whole blood, w is whole-body hematocrit, mic is microcirculation, sys is macrocirculation, and rbc is red cell mass (14).

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