Relative Blood Volume Changes Underestimate Total Blood Volume Changes during Hemodialysis

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Background: Measurements of relative blood volume changes (ΔRBV) during hemodialysis (HD) are based on hemoconcentration and assume uniform mixing of erythrocytes and plasma throughout the circulation. However, whole-body hematocrit (Ht) is lower than systemic Ht. During HD, a change in the ratio between whole-body to systemic Ht (F cell ratio) is likely to occur as a result of a net shift of low Ht blood from the microcirculation to the macrocirculation. Hence, ΔRBV may differ significantly from total blood volume changes (ΔTBV). Therefore, this study compared ΔRBV and ΔTBV during HD.

Design, participants, and measurements: Plasma and erythrocyte volumes were measured using 125I- and 123I-radioiodinated albumin and 51Cr-labeled erythrocytes, respectively. After validation of the standardized method in two patients on a nondialysis day, seven patients completed the protocol during HD. 125I-albumin and 51Cr-labeled erythrocytes were administered 20 min before the start of HD. 123I-albumin was administered at 160 min into the HD session to quantify and correct for 125I-albumin leakage. ΔRBV was measured continuously throughout HD. The F cell ratio was derived from whole-body and systemic Ht.

Results: Total ultrafiltration volume was 2450 ± 770 ml. TBV declined from 5905 ± 824 to 4877 ± 722 ml during HD. Thus, TBV declined 17.3 ± 4.4%, whereas the RBV decline was only 8.2 ± 3.7% (P = 0.001). The F cell ratio increased from 0.896 ± 0.036 to 0.993 ± 0.049 during HD (P = 0.002).

Conclusions: ΔRBV significantly underestimates ΔTBV during HD. The rise in F cell ratio strongly suggests that during HD, blood translocates from the microcirculation to the macrocirculation, probably as a cardiovascular compensatory mechanism in response to hypovolemia.


Technological advances have allowed the development of continuous, noninvasive measurement of relative blood volume changes (ΔRBV) during hemodialysis (HD). Continuous registration of ΔRBV during HD with ultrafiltration (UF) is advocated as a tool to maintain an adequate volume of the intravascular compartment to avoid HD hypotension (1–3). However, the use of ΔRBV measurements in clinical practice depends on its accuracy in reflecting the change in whole-body blood volume or total blood volume (ΔTBV).

Noninvasive measurements of ΔRBV are based on hemoconcentration of blood constituents that remain in the circulation during HD with UF. Mostly erythrocytes are used for these measurements. ΔRBV devices that are based on hemoconcentration of afferent blood can adequately represent ΔTBV only in case of uniform mixing of plasma and erythrocytes throughout the different vascular beds of the circulation (4–6). However, this assumption is not valid: The whole-body hematocrit (Ht) is lower than the Ht of arterial or venous blood (7,8). The difference is due to a dynamic reduction in microvascular Ht in capillaries and venules (<200 μm), known as the Fahraeus effect (9). The difference between arterial or venous Ht and whole-body Ht is expressed as the F cell ratio (the ratio of whole-body Ht to arterial or venous Ht) and approximates 0.91 in nondialysis individuals (10,11). The lack of uniform mixing of erythrocytes throughout the circulation would not induce a divergence between ΔRBV and ΔTBV calculation if the difference in Ht between the different vascular beds would remain constant during HD—in other words, if the F cell ratio would not change (12). However, a change in F cell ratio may occur during HD with UF (13,14). As a consequence, the observed ΔRBV may differ significantly from the ΔTBV (13).

To our knowledge, no studies to date that have compared absolute ΔTBV, which is the sum of erythrocyte and plasma volume, using methods that are generally accepted as the gold standard: Radiiodinated albumin (125I) and 51Cr-labeled erythrocytes (15,16), during HD with UF with its relative counterpart: ΔRBV measurements as measured by hemoconcentration of afferent blood. In this study we compared hemoconcentration-based ΔRBV and ΔTBV measured by repetitive measurement of
Materials and Methods

Patients

The standardized method for determining plasma and erythrocyte volumes (radioiodinated $^{125}$I-albumin and $^{51}$Cr, respectively) was evaluated for its stability for repeated measurements in two HD patients on a nondialysis day in a prestudy test. Subsequently, eight patients underwent measurements of absolute plasma and erythrocyte volumes during a single HD session according to the same protocol.

To be eligible, patients had to fulfill the following criteria: (1) Non-hypotension-prone male HD patients who were treated with HD for at least 6 mo and had stable values for hemoglobin (>7 mmol/L); (2) unaltered erythropoietin dosage for at least 2 mo; (3) an arteriovenous fistula without recirculation as established by Transonic flow measurements (Transonic Systems, Ithaca, NY); and (4) no residual renal function (diuresis <100 ml/24 h). Exclusion criteria were (1) the absence of informed consent, (2) Recent hemorrhage, and (3) diabetes. The last exclusion criteria was applied because participating patients were not allowed to eat or drink during the study.

Study Protocol

Determination of Erythrocyte and Plasma Volume. Plasma and erythrocyte volume measurements are routinely used to assess erythrocyte and plasma volume in the diagnosis of polycythemias. The principle is based on the so-called “isotope dilution technique.” Volumes are calculated from the known dosage administered and the radioactivity concentration measured in whole blood or plasma (15). A single dose of $^{51}$Cr-labeled erythrocytes will suffice for the duration of this study because the radioactivity half-life is 28 d.

Because transcapillary albumin leakage occurs in both healthy control subjects and HD patients (17), it is not possible to measure reliably the plasma volume over a longer period of time when using only one radioiodinated marker. We therefore determined plasma volume using two radioiodinated albumin injections. We chose $^{125}$I-albumin and $^{123}$I-albumin because these isotopes differ in $\gamma$-ray energy (27 to 32 and 159 keV, respectively) and, thus, allow separate detection in the $\gamma$ counter. The administration of the second radioiodinated isotope, 180 min after administration of the first isotope, allows quantification of and correction for the transcapillary escape rate of albumin (TER$_{\text{alb}}$). The quantification of TER$_{\text{alb}}$ was based on the first $^{125}$I plasma volume measurement and the $^{125}$I plasma volume determination after 180 min of HD because at this point in time, the plasma volume as assessed simultaneously by $^{125}$I and $^{123}$I should yield identical results. In this study, we assumed that TER$_{\text{alb}}$ was constant during HD in the individual participant. All values for plasma volume displayed in this study are corrected for TER$_{\text{alb}}$.

Radioiodination of erythrocytes and $^{123}$I-albumin labeling were performed under aseptic conditions in the radiopharmacy unit of the Nuclear Medicine Department under supervision of a hospital pharmacist. $^{51}$Cr-sodium chromate and $^{123}$I-sodium iodide ($^{123}$I-Nal) were obtained from GE Health (Eindhoven, Netherlands). $^{125}$I-human serum albumin ($^{125}$I-HSA) was obtained from Merck Frosst Canada (Kirkland, Q, Canada).

An extensive description of the used methods is described in detail elsewhere (15,16). In short, the $^{51}$Cr-sodium chromate solution was added to the patients’ erythrocytes. The mixture was incubated for 45 to 60 min at a temperature of 37°C. Thereafter, 25 mg of ascorbic acid was added to the labeled erythrocyte suspension. A known amount of the well-mixed labeled erythrocyte suspension was injected together with a known amount of $^{125}$I-HSA to the patient.

HSA (Ceaib 20%; Sanquin, Amsterdam, Netherlands) was labeled in the radiopharmacy department with $^{125}$I-Nal using a standard iodogen (Pierce Biotechnology, Rockford, IL) method. The mixture was purified over a PD-10 column (Sephadex G-25M; Amersham Biosciences AB, Uppsala, Sweden) and overnight dialysis (Slide-A-Lyzer; Pierce Biotechnology). Radiochemical purity was >98%.

Protocol. The study protocol was identical during the prestudy test and the HD study except for the start of HD (T = 0) during the latter study. HD commenced 20 min after the first injection with the radiopharmaceuticals. This time interval was chosen to allow adequate distribution of the radioiodinated isotopes (15,16). For avoidance of the widely known influence of postural changes on blood volume (18) and F cell ratio (19,20), patients were placed in a supine position 20 min before blood sampling for erythrocyte labeling with $^{51}$Cr and remained in this position until the study protocol was completed (from 100 min before the start of HD until the stop of HD). After completion of the erythrocyte labeling with $^{51}$Cr, the patients’ own blood supplemented with $^{125}$I-albumin was administered. The interval between blood sampling for the labeling of the erythrocytes and the re-administration of the isotopes was 60 min. During the prestudy test and the HD study, $^{125}$I was given 180 min after the administration of $^{125}$I (160 min into the HD session). Blood was sampled four times at 10-min intervals immediately after both injections that contained the isotope(s). After four blood samples, the interval between two samplings was increased to 20 min. In total, blood was sampled 17 times. At each sampling, a total of 5.5 ml of blood was withdrawn. Each sampling included erythrocyte and plasma volume calculation as well as determination of whole-body and systemic Ht. Because the average Ht in our patient group was $0.40 \pm 0.05$ at the start of HD, the sampling of a total of 93.5 ml of blood equals an erythrocyte and plasma volume of approximately 37.4 and 56.1 ml, respectively. In the calculations of erythrocyte and plasma volume, we made no corrections for this sampling of blood because this plasma volume is very small in comparison with the expected change in plasma volume and because this erythrocyte volume is negligible compared with the patients’ erythrocyte volume. A standard dialysis needle was used for blood sampling. A vein on the nondialysis access side was cannulated for the purpose of administering the radiopharmaceuticals.

Patients were asked to refrain from coffee, tea, alcohol, and tobacco use from the night before the study until completion of the study. With the exception of a glass of water (125 ml) at room temperature after 20 and 200 min into the HD session, patients were not allowed to eat or drink throughout the study to avoid any influence of food intake on blood volume (21). BP and heart rate were measured simultaneously during each time blood was sampled.

The study was approved by the Medical Ethics Committee of the University Medical Center Groningen. Written informed consent was obtained from all participating patients. The study was performed in accordance with the principles of the Declaration of Helsinki and guidelines for Good Clinical Practice.

Dialysis Settings. All eight patients underwent dialysis for 4 h with bicarbonate dialysis in a single session. A low-flux polysulfone hollow-fiber dialyzer (F8; Fresenius Medical Care, Bad Homburg, Germany) was used. Blood flow rates and dialysate flow rates were set at 250 and 300 ml/min, respectively. Dialysate composition was as follows: Sodium 139 mmol/L, potassium 1.0 mmol/L, calcium 1.5
mmol/L, magnesium 0.5 mmol/L, chloride 108 mmol/L, bicarbonate 34 mmol/L, acetate 3.0 mmol/L, and glucose 1.0 g/L. Dialysate temperature was set at 36.0°C. HD was performed with the Integra HD apparatus (Gambro-Hospal, Lyon, France). ΔRBV were measured with Hemoscan (Gambro-Hospal). In addition, we assessed ΔTBV from changes in Ht (ΔRBV-Ht) in afferent blood because this method is considered to be the reference method for determining ΔRBV during HD (5,22).

Calculations
The following calculations were used in this study:

- Total blood volume = erythrocyte volume + plasma volume
- Whole-body Ht = erythrocyte volume/(erythrocyte volume + plasma volume)
- F cell ratio = whole-body Ht/venous Ht

ΔTBV (in %) = [(TBV₀ − TBVᵣ)/TBV₀] × 100
ΔRBV-Ht (in %) = [(Ht₀/Htᵣ) − 1] × 100

in which TBV₀ and Ht₀, and TBVᵣ and Htᵣ represent TBV and Ht at the start of HD and at a certain moment during HD, respectively.

Statistical Analyses
All data were analyzed using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA). Data are presented as mean ± SD unless stated otherwise. Comparisons were made with a paired t test or an unpaired t test when appropriate. In addition, Bland-Altman analysis was used for the evaluation of differences between ΔRBV and ΔTBV. From these results, the Pearson correlation coefficient r was derived. P < 0.05 was considered significant.

Results
Patients
Patient characteristics of the two patients in the prestudy test were as follows: Age 67 and 62 yr; dialysis vintage 2 yr and 9 mo and 13 yr, respectively. Cause of renal failure was hypertension and IgA nephropathy, respectively. Plasma volume was 2086 and 2331 ml at the start of the study and 2092 and 2357 ml at the stop of the study for patients 1 and 2, respectively. Erythrocyte volume was 2086 and 2331 ml at the start of the study and 2064 and 2327 ml at the stop of the study for patients 1 and 2, respectively. The studies in both patients finished the protocol that consisted of plasma and erythrocyte measurements during HD with UF. The results from one patient were excluded from analysis because the erythrocyte volume was unstable.

Patient characteristics of the seven patients from the HD study were as follows: Mean age 56 ± 20 yr (range 27 to 74 yr). The mean time on dialysis was 3.1 ± 1.9 yr (range 1 to 6 yr). The cause of renal failure was hypertension (n = 4), chronic pyelonephritis (n = 1), membranoproliferative glomerulonephritis (n = 1), and Wegener’s granulomatosis (n = 1). Pre- and post-HD weight was 74.8 ± 8.6 and 72.4 ± 8 kg, respectively. Pre- and post-HD systolic BP was 134 ± 13 and 130 ± 20 mmHg, respectively. Pre- and post-HD diastolic BP was 77 ± 17 and 75 ± 14 mmHg, respectively. Heart rate was 65 ± 9 before HD and 70 ± 15 bpm after HD. No hypotensive episodes occurred during any of the HD sessions.

Erythrocyte and Plasma Volume
In Table 1, the erythrocyte and plasma volumes are shown for the individual patients throughout the HD session. In addition, the individual data for TBV, UF volume, and TERᵣₑ are displayed. No significant changes in erythrocyte volume were found. Plasma volume declined from 3784 ± 648 at the start of HD to 2741 ± 563 ml at the end of HD (P = 0.0001). TBV declined from 5905 ± 824 at the start of HD to 4877 ± 722 ml at the end of HD (P = 0.0001). Mean total UF volume was 2450 ± 770 ml. Mean TERᵣₑ was 9.1 ± 1.3%/h.

Table 2 shows the individual change in both TBV and RBV throughout the HD session. In all patients, ΔRBV underestimated the decline in TBV during the second half of the HD session. Figure 1 shows the mean course of ΔTBV and ΔRBV throughout the study. TBV declined 17.3 ± 4.4% at the end of HD, whereas the observed RBV decline was only 8.2 ± 3.7% (P = 0.001). The difference between ΔTBV and ΔRBV was significant (P < 0.05) from 120 min onward. ΔRBV-Ht yielded identical results to ΔRBV (data not shown). There was consid-

Table 1. EV, PV, TBV, UF, and transcapillary escape rate of albumin in the individual patients

<table>
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<th>Patient</th>
<th>EV (ml)</th>
<th>PV (ml)</th>
<th>TBV (ml)</th>
<th>UF (ml)</th>
<th>TERᵣₑ (%)/h</th>
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0 min and 240 min denote the start and end of the hemodialysis session, respectively. EV, erythrocyte volume; PV, plasma volume; TBV, total blood volume; TERᵣₑ, transcapillary escape rate of albumin; UF, ultrafiltration.
Table 2. ΔTBV and ΔRBV at hourly intervals in the individual patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>ΔTBV (%) 60 min</th>
<th>ΔTBV (%) 120 min</th>
<th>ΔTBV (%) 180 min</th>
<th>ΔTBV (%) 240 min</th>
<th>ΔRBV (%) 60 min</th>
<th>ΔRBV (%) 120 min</th>
<th>ΔRBV (%) 180 min</th>
<th>ΔRBV (%) 240 min</th>
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<td>-13.1</td>
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</tbody>
</table>

*ΔRBV, change in relative blood volume; ΔTBV, change in total blood volume.

Figure 1. The mean course of total blood volume changes (ΔTBV; ○) and relative blood volume changes (ΔRBV; ●) during hemodialysis (HD) of the seven patients. Data are means ± SD. *P < 0.05 versus the start of the HD session.

Figure 2. Bland-Altman plots comparing ΔRBV and ΔTBV at 60, 120, 180, and 240 min into the HD session. Reference lines indicate mean difference ± 95% limit of agreement. Correlation between difference and average: r = 0.42 (P = 0.0002). A difference above zero indicates that ΔRBV overestimates ΔTBV; a difference below zero indicates that ΔRBV underestimates ΔTBV. ●, patient 1; ○, patient 2; ▽, patient 3; ♦, patient 4; *, patient 5; □, patient 6; △, patient 7.

erable interindividual variation in the magnitude of the difference between ΔRBV and ΔTBV (Figure 2). Overall, bias was −5.2% with a 95% limit of agreement from −13.7 to 3.4%. A significant correlation was found when the difference and average of ΔRBV and ΔTBV were compared: r = 0.42 (P = 0.0002). The extent of the difference between ΔRBV and ΔTBV did not differ between the patients with a UF volume <2450 ml (n = 3; mean −5.3 versus −13.9%) in comparison with the four patients with a UF volume >2450 ml (n = 4; mean −10.4 versus −19.9%).

F Cell Ratio

In all patients the F cell ratio rose during HD (Table 3). The difference between the F cell ratio at the start of HD in comparison with the F cell ratio during HD was significant (P < 0.05) from 60 min into the HD session onward (Figure 3). The F cell ratio increased from 0.896 ± 0.036 at the start of HD to 0.993 ± 0.049 at the stop of the HD session (P = 0.002).

Discussion

This study shows directly that ΔRBV as assessed by hemoconcentration of afferent blood significantly underesti-
Table 3. Individual hourly F cell ratios

<table>
<thead>
<tr>
<th>Patient</th>
<th>F Cell Ratio</th>
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</tr>
<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
<td>0.92</td>
</tr>
<tr>
<td>4</td>
<td>0.95</td>
</tr>
<tr>
<td>5</td>
<td>0.90</td>
</tr>
<tr>
<td>6</td>
<td>0.87</td>
</tr>
<tr>
<td>7</td>
<td>0.88</td>
</tr>
<tr>
<td>Mean</td>
<td>0.896</td>
</tr>
</tbody>
</table>

Figure 3. The mean course of the F cell ratio (●) during HD of all seven patients. *p < 0.05 versus the start of the HD session.

would not change (19,23). This study, however, clearly demonstrates that the F cell ratio increases markedly during HD. We hypothesize that this reflects translocation of blood with a lower Ht from the microcirculation to the macrocirculation, thereby inducing a dilution of the central blood compartment. Therefore, the hemoconcentration of blood that reaches the ΔRBV monitor is not representative of the hemoconcentration of the TBV. As a result, ΔRBV monitors underestimate the real ΔTBV during HD.

Mitra et al. (13) indirectly established that the F cell ratio might rise during HD. These authors used Indocyanine green to determine plasma volume. Erythrocyte volume was subsequently calculated from plasma volume and venous Ht. However, the use of calculated erythrocyte volumes necessitates the input of an estimated average F cell ratio because an individual F cell ratio cannot be derived from plasma volume alone. This may induce an error because population values for the F cell ratio have been reported as 0.864 (24) and 0.91 (25). On an individual level, F cell ratios have been reported to display wide scattering from 0.76 to 1.15 (25). Therefore, the input of a mean F cell ratio for different patients may introduce a substantial error in calculating erythrocyte volumes in patients who have an F cell ratio that differs from the mean value (15,25). In our study, the mean pre-HD F cell ratio differed from the mean population values mentioned. In addition, our patients displayed a wide interindividual variability in F cell ratio (from 0.84 to 0.95 before HD). Nevertheless, our study does support the hypothesis from Mitra et al. In their study, they could not explain the apparent rise in erythrocyte volume other than by an increase in F cell ratio during HD with UF (13). Our direct F cell measurements underline this hypothesis. It is interesting that the difference between ΔRBV and ΔTBV that we found was of the same order of magnitude as in the study of Mitra et al. (8.2 ± 3.7 and 7.7 ± 10.6%, respectively).

In this study, we used 123I-albumin as a second plasma volume marker to quantify and correct for TERalb from 125I-albumin during HD. In healthy control subjects, TERalb has been demonstrated to range from 4.3 to 7.4%/h (17,26–28). Hildebrandt et al. (17) showed a mean TERalb of 9.6% in HD patients before the start of HD, and Geers et al. (26) found a TERalb of 9.8 ± 2.6% in patients with the nephrotic syndrome. As a mean, we found an intradialytic TERalb of 9.1 ± 1.3%, which is in line with the aforementioned studies.

This study has some important pathophysiologic and clinical implications. It shows directly that the F cell ratio rises during HD. This observation strongly suggests that during HD, translocation of blood from the microcirculation to the macrocirculation takes place, which probably is a cardiovascular compensatory mechanism in response to hypovolemia. The underestimation of the real TBV decline may explain why some patients develop hypotension at a relatively small RBV decline. In addition, the poor predictive value of ΔRBV for the occurrence of dialysis hypotension (reviewed by Dasselaar et al. [12]) may well partly be explained by variability in the divergence between ΔRBV and ΔTBV (and thus a variable rise in F cell ratio) during HD. In this study, the extent of the divergence between ΔRBV and ΔTBV indeed differed considerably between individuals. Some patients displayed a relatively small difference between ΔRBV and ΔTBV (e.g., −12.2 versus −14.0% in patient 7), whereas others displayed a substantial difference (e.g., −8.1 versus −22.8% in patient 3). Notably, the divergence between ΔRBV and ΔTBV was of the same order of magnitude in patients with a relative low and high UF volume. In other words, the difference between ΔRBV and ΔTBV was also prominent in the patients with relatively low UF volumes (e.g., −5.7 versus −14.3% with a UF volume of 1200 ml in patient 2).

Factors that may influence the extent of the intradialytic translocation of blood from the microcirculation to the macrocirculation (and thus the extent of the change in F cell ratio) are ambient and dialysate temperature, changes in position, administration of vasoactive drugs and exercise during HD. All of these factors are known to influence ΔRBV (reviewed in reference [12]). It remains to be studied whether these factors also influence ΔTBV and/or the divergence between ΔRBV and ΔTBV.

In this study, we investigated hemodynamically stable patients. Future studies should also address the issue of underestimation of ΔTBV by ΔRBV and the change in F cell ratio in hypotension-prone HD patients. For the moment, however, it is important for the dialysis staff to realize that the relative change in blood volume, as calculated by ΔRBV monitors, may mark-
edly underestimate the real decline in blood volume, especially in the second half of the HD session.

Conclusion

ΔRBV significantly underestimates ΔTBV during HD. The rise in F cell ratio strongly suggests that blood translocates from the microcirculation to the macrocirculation during HD, probably as a cardiovascular compensatory mechanism in response to intravascular volume depletion.

Acknowledgments

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Disclosures

None.

References