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Radioisotope blood volume measurement in hemodialysis patients

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Abstract

Accurate assessment of blood volume (BV) may be helpful for prescribing hemodialysis (HD) and for reducing complications related to hypovolemia and volume overload. Monitoring changes in relative BV (RBV) using hematocrit, e.g., Crit-Line Monitor (CLM-III), an indirect method, cannot be used to determine absolute BV. We report the first study of BV measurement for assessing volume status in HD patients using the indicator dilutional method. Ten adult HD patients were enrolled in this prospective observational study. BV measurement was performed before and after HD using BV analysis (BVA)-100 (Daxor Corporation, New York, NY, USA). BVA-100 calculates BV using radiolabeled albumin (Iodine-131) followed by serial measures of the radioisotope. Fluid loss from the extravascular space was calculated by subtracting the change in BV from total weight loss. Intradialytic changes in RBV were measured by CLM-III. Eight out of 10 cases had significant hypervolemia, two cases were normovolemic. The range of BV variation from predicted normal was 156 to 1990 mL. Significant inter-individual differences in extravascular space fluid loss ranged from 54% to 99% of total weight loss. Spearman correlation showed a good correlation in the measurement of RBV by BVA-100 and CLM-III in 8 out of 10 patients ($r^2 = 0.64$). BV measurement using BVA-100 is useful to determine absolute BV as well as changes in BV and correlates reasonably well with CLM-III measurements. Individual refilling ability can be determined as well. This may prove useful in prescribing and monitoring ultrafiltration rates, establishment of optimal BV in HD patients and reducing morbidity and mortality associated with chronic HD.

Key words: Blood volume determination, absolute blood volume, hemodialysis, ultrafiltration, dry weight

INTRODUCTION

One of the functions of hemodialysis (HD) is the removal of extracellular fluid (ECV) that accumulates as a result of kidney failure. The ECV fluid has two components: intravascular (IV) and interstitial (IS). Accurate determination of fluid changes that occur during HD with ultrafiltration (UF) is essential for determining the efficacy of HD, as well as for reducing associated complications. Excess volume removal during HD can lead to complications such as hypotension,[1] cramping and increased risk of vascular access thrombosis.[2] HD-induced hypotension is associated with cardiac-wall-motion abnormalities and stunning.[3,4] In contrast, if patients do not have sufficient UF to achieve their target dry weights (DW), they are at risk of remaining in a state of chronic

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volume overload, which may lead to hypertension,[5] left ventricular hypertrophy,[6] and congestive heart failure.[7] In fact, inadequate UF may contribute to the fact that cardiovascular disease is the major cause of mortality and morbidity among patients receiving long-term dialysis therapy.[8,9] In recent studies, the mortality of patients on HD is highest in the first year after initiation of HD.[10] It is possible that some of this mortality is related to attempts to determine and achieve DW, resulting in large hemodynamic shifts.

The assessment of volume status and DW in HD patients remains a clinical judgment. Clinical assessment of volume status and measured blood volume (BV) analysis have been shown to be concordant in only 51% of cases.[11] Agarwal[12] defined DW as the lowest tolerated postdialysis weight achieved by gradual reduction and at which there are minimal signs or symptoms of hypovolemia or hypervolemia. In a prospective randomized controlled trial by Agarwal et al.,[13] additional UF beyond prescribed DW in HD patients achieved a statistically significant reduction in blood pressure (BP).

Noninvasive measures of volume assessment such as echocardiographic measurement of inferior vena caval diameter[14] and bioimpedance[15] have not been proven to be beneficial in the assessment of DW. To aid in the accurate assessment of ECV, several devices have been developed that monitor changes in BV during HD. These devices indirectly monitor changes in relative BV (RBV), utilizing changes in either the hematocrit (Hct)[16] or the total plasma protein concentration.[17] An example of such a device is the Crit-Line Monitor (CLM III; Hema Metrics, Kaysville, UT, USA). While several observational studies have shown improved outcomes for end-stage renal disease (ESRD) patients using Hct as a surrogate for BV,[16,18,19] a large, randomized trial did not show a beneficial outcome.[20] It has been shown that changes in RBV tend to underestimate total BV changes during HD.[13,21]

Direct BV analysis (BVA) identifies absolute BV deficits and excesses relative to deviations from an ideal, which is individually calculated for each patient based on his or her body habitus.[22,23] BVA has been utilized for estimation of BV in patients with congestive heart failure[11] and patients admitted to critical care unit to guide fluid therapy.[24] We measured BV in a group of HD patients using BVA-100 (Daxor Corporation) before and after HD, and correlated the results with CLM-III measurements and changes in weight. This is the first study looking at the analysis of absolute BV in HD patients and its correlation with DW.

MATERIALS AND METHODS

Patients

Ten adult patients on chronic maintenance HD at New York Harbor Veterans Affairs Healthcare System (VA-NYHHS) were selected to undergo BVA pre and post-HD on their regular dialysis day. We included patients aged 21 years or older with ESRD on chronic HD for at least 6 months. We excluded patients with known hypersensitivity to iodine, eggs, albumin, or any other component of the Volumex injection kit. Patients expecting to receive kidney transplant in the next 6 months, those with a malignancy requiring chemotherapy, those whose BP could not be obtained with a sphygmomanometer, those with active hematological disease or active gastrointestinal bleeding, or those with predialysis serum albumin less than 2.6 g/dL were all excluded. Patients with persistent intradialytic BP instability (hypotensive episodes in >80% of regular dialysis sessions) within the previous 1-month period were also excluded. Patients were excluded if they had a life expectancy of less than 1 year, if they were non-ambulatory, or if they could not comply with additional protocol lab measurements before and after their dialysis session.

Each patient underwent a screening visit during which medications and other comorbid conditions were reviewed. A written informed consent with regard to the use of radioactive diagnostic tracer and blood collection was obtained. They were given a prescription for saturated solution of potassium iodide (SSKI) for thyroid iodine uptake blockade. The Food and Drugs Administration has approved the dose of 130 mg/d (one drop twice a day of SSKI mixed in 8 oz of water). Study subjects took SSKI beginning on the day before the procedure and continued it for 7 days after the BVA was completed. The study was approved by the local institutional review board and registered with Clinicaltrials.gov (NCT01679249). The sponsor advised us regarding the use of the BVA-100, but was not involved with the analysis of the data or the preparation of the article.

Dialysis protocol

HD was performed on 10 patients using a Phoenix® delivery system (Gambro, Stockholm, Sweden) and polyamide Polyflux 210 dialyzers (Gambro) or Rexeed 25SX dialyzers (Asahi Kasei Medical Co., Tokyo, Japan). Patients were weighed before and after dialysis, with the difference taken as the volume of ultrafiltrate removed. Vital signs monitoring was performed according to unit protocol. All patients underwent their usual, prescribed

dialysis treatments. Standard bicarbonate dialysate was used in each treatment. Blood flow rates were maintained at the prescribed level, typically between 400 and 500 mL/min. Blood samples were obtained from the venous end of the dialysis access. Laboratory work obtained for each patient included: (i) peripheral hemoglobin and Hct (Hct_P); (ii) plasma sodium concentration; and (iii) serum albumin concentration. These samples were processed at the local laboratory. Additional clinical information recorded during each dialysis session included: (i) occurrence of any hypotensive episodes that require medical intervention (i.e., cessation of UF, saline administration, or changes in body position); and (ii) occurrence of any signs and symptoms associated with hypovolemia (dizziness, weakness, nausea, muscle cramps, blurred vision, fatigue, thirst, and/or loss of consciousness) regardless of changes in BP.

Determination of RBV change using CLM-III

All HD treatments were done with the CLM-III device, measuring changes in Hct (Hct_C) via an optical sensor on the dialysis circuit. The CLM-III yields a continuous recording of Hct_C in response to UF. The CLM-III is manufactured with the capability to detect Hct_C of 0.1% and very low signal noises, and these features are routinely validated at the Hema Metrics blood laboratory.

Determination of absolute plasma volume (PV) and BV

BV measurement with the BVA-100 uses the principle of indicator dilution to obtain data on total BV, red blood cell volume and PV. It predicts normal BV for a given individual on the basis of his or her deviation from ideal body weight.[22,23] BVA-100 also provides a variable called normalized Hct (Hct_N) in which the peripheral Hct has been adjusted for volume derangements. Each patient underwent two radioisotopic BV measurements; the first measurement was performed approximately 1 hour before HD and the second was performed immediately following the end of the HD session. The average time delay between noting the post-HD CLM-III BV estimate and sampling for measurement of post-HD BVA PV was 10–15 minutes.

Samples for BVA were obtained from the venous end of the dialysis access. BVA was performed as follows: a blood sample (5 cc) was obtained for background radioactivity count. A known amount of tracer (Iodine-131, 25 μCi) was administered. Complete mixing occurred in the following 10–12 minutes. Six blood samples were drawn at serial intervals of 4–6 minutes each. The volume of each blood sample was 5–6 cc. Serial samples allow estimation of transudation from the IV space into the IS. BV was determined by BVA-100 under aseptic conditions in the Nuclear Medicine department of the VA-NYHHS. Various variables were calculated as follows:

$$PV = \frac{1000 \times (\text{standard count} - \text{baseline count})}{(\text{sample count} - \text{baseline count})}$$

$$BV = \frac{PV}{1 - (\text{Hct} \times f0.91 \times 0.99)}$$

$$f = \text{F-cell ratio} \quad \text{Hct}_p / \text{Whole body hematocrit}$$

BVA-100 calculates BV with an accuracy of ± 2.5%. The absolute BV change for each dialysis session was obtained by subtracting the pre-HD BV from the post-HD BV. Another important value that can be calculated from BVA-100 is the volume of ultrafiltrate derived from IV space (UF_{IV}). The volume of ultrafiltrate contributed by the EV-IS (UF_{IS}) can be calculated by subtracting fluid removal from IV space from the total UF volume (UF_T).

Storage and preparation of the radiolabeled albumin, and counting and disposal of the blood samples, was performed by the Nuclear Medicine department. The injection is estimated to provide approximately 100 mrem (1 mSv) per 25 microcurie dose, approximately equivalent to a year's dose from cosmic radiation in New York. Dialysis personnel and other dialysis patients are therefore not considered at risk for any meaningful increase in radiation exposure.

Hct_N

With a direct BV measurement, however, it is possible to calculate Hct_N. This is the Hct that would result if the patient's BV is adjusted by a PV change so that the patient had a normal BV. Hypervolemic patients will have Hct_N that is higher than their peripheral Hct. Normovolemic patients will have a Hct_N that is relatively similar to the peripheral Hct, while hypovolemic patients will have a Hct_N that is significantly lower than the peripheral Hct.

Statistical analysis

Statistical analysis was performed using Spearman rank–order correlation coefficient method using the Statistical

Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). A P value of < 0.05 was considered significant.

RESULTS

Between September 2011 and March 2012, 10 patients on chronic-maintenance HD were recruited from the outpatient dialysis unit of the NYHHS. Clinical characteristics of the 10 HD patients in the study are presented in Table 1. The clinical characteristics of the group are reflective of the patient population served by the NYHHS. The mean estimated DW pre-HD and post-HD weight of the group was 79.1 ± 11.03 kg, 82.9 ± 11.0 kg and 80.5 ± 11.1 kg, respectively. Mean UF volume was 3192 ± 951.9 mL while mean urea reduction ratio was 75%.

BV analysis using BVA-100

Table 2 shows the results of BV analysis pre-HD and post-HD in 10 HD patients. There was heterogeneity among the 10 cases prior to dialysis treatment. Eight out of 10 patients were hypervolemic (pre-HD BV ranged from 8% to 44% above their ideal BV), while two were normovolemic. Post-HD, six of the eight volume-overloaded continued to have BV from 6% to 37% above their calculated ideal BV, with patients 1, 2, 6, and 7 showing significant hypervolemia post-HD despite UF. Majority of these six patients continued to be either hypertensive post-HD or had intradialytic hypertension, indicative of persistent volume overload. Patients 3, 5, and 9 showed a reduction in BV below their individual calculated ideal values (range –4% to –12 %) without manifesting signs or symptoms of hypovolemia. Patient 8 also showed reduction in BV below the calculated ideal BV and had positive orthostatic vital signs post-HD. There was no correlation between BP and degree of volume excess pre-HD (data not shown).

As shown in Table 2, majority of patients (n = 9) had a large portion of UF volume derived from the EV-IS compartment (range 54%–106%, median 81%). Although, there was a trend toward an increase in post-HD albumin levels (when compared with pre-HD albumin), the percentage change in post-HD albumin did not always correspond to percentage decrease in intradialytic BV.

Comparison between BV changes obtained using BVA-100 vs. CLM-III

Table 3 shows the values of BV changes obtained using BVA-100 and CLM-III for 10 study subjects. In 8 out of 10 patients, changes in BV using BVA-100 are either similar to or greater than the changes in BV obtained using CLM-III. Figure 1 shows a good correlation between BV changes obtained using the two modalities. For most patients, the expected relationship between the relative and absolute BV changes held true.

However, there were exceptions. Patients 4 and 6 showed discordance between the BV values obtained

Table 1 Patient characteristics (mean ± SD where applicable)

Age (years)	65 ± 9.9
Height (meters)	1.7 ± 0.07
BMI (kg/m^2)	28.6 ± 3.7
Pre-HD mean SBP	138 ± 24
Pre-HD mean DBP	71.7 ± 10.4
Post-HD mean SBP	135.5 ± 13.6
Post-HD mean DBP	73.5 ± 10.4
Men (N)	10
Race (N)	
White	2
African-American	5
Hispanic	3
Etiology of end-stage renal disease (N)	
Diabetes	4
Unknown	3
HIV	2
Atheroembolic disease	1
Men (N)	10
Race (N)	
White	2
African-American	5
Hispanic	3
Comorbidities (%)	
Diabetes mellitus	50
Hypertension	90
Congestive heart failure	30
Coronary artery disease	50
Cerebral vascular disease	10
Peripheral vascular disease	10
Anti-hypertensive medications (%)	
Beta-blockers	90
RAAS inhibition	60
Calcium channel blockers	60
Diuretics	40
HD access (N)	
AVF	9
AVG	1

All means ± SD.
AVF = arteriovenous fistula; AVG = arteriovenous graft; DBP = diastolic blood pressure; HD = hemodialysis; RAAS = renin-angiotensin-aldosterone system; SBP = systolic blood pressure; SD = standard deviation.

Table 2 BVA-100 DATA (along with data on pre-HD serum albumin and intradialytic change in serum albumin)

Patient	EDW (kg)	UF_T (mL)	Ideal BV_{BVA} (mL)	BV_{BVA} (mL)		Change from ideal BV(%)		UF_{IS} (mL) (UF_T-UF_{IV})	UF_{IS} UF_T (%)	Pre-HD Alb. gm/dL	Δ Alb. (%)[a]
				Pre-HD	Post-HD	Pre-HD	Post-HD				
1	83	3400	5182	7023	6386	35	23	2763	81	3.6	+11
2	76	1500	4707	5945	5500	26	17	1055	70	3.9	+7
3	76	3100	4603	5191	4345	12	–7	2254	72	3.8	+13
4	83	1600	5081	5335	5438	5	7	1703	106	3.8	+8
5	57	2100	4309	4637	4213	8	–4	1676	79	4.2	+2
6	74	2800	4901	6940	5654	41	15	1514	54	3.8	+8
7	80	3800	5610	8052	7703	44	37	3451	90	3.7	+3
8	97	2300	5397	5605	5578	4	–3	2273	98	4.2	+7
9	92	500	5037	4827	4422	–4	–12	95	19	4.1	–5
10	72.5	2400	4481	5602	5154	25	15	1952	81	3.9	+13

[a] $\frac{[(\text{Post HD}) - (\text{Pre HD})]\ \text{Albumin}}{\text{Pre-HD Albumin}} \times 100$

Alb = albumin; BV_{BVA} = blood volume measurement using blood volume analyzer; EDW = estimated dry weight; HD = hemodialysis; UF_{IS} = ultrafiltration from extravascular space; UF_{IV} = ultrafiltration from intravascular space; UF_T = total ultrafiltration.

using BVA-100 and CLM-III. Specifically, according to BVA-100, patient 4 gained 1.9% in BV after dialysis despite UF causing loss of 1.6 kg. CLM-III demonstrated the expected increase in Hct_C corresponding to the observed UF. On the other hand, despite a 46% decrease in absolute BV according to BVA-100, the change in RBV measured by CLM-III was minimal. If patients 4 and 6 are included in the analysis, the correlation between the two modalities shows no correlation ($r^2 = 0.01$).

Table 3 Intradialytic change in BV using CLM III vs. BVA-100

Patient	ΔBV_{BVA} (%)	$\Delta BV_{CLM\text{-}III}$ (%)	ΔHct_P	ΔHct_C
1	10	7.7	5.2	2.8
2	9.3	10.4	2.1	3.3
3	19.5	19.6	3.2	7.3
4[a]	–1.9	13	2.8	4.2
5	10.1	8.8	2	2.9
6[a]	22.7	4.2	0.7	1
7	4.5	3.9	1.2	1.1
8[b]	0.5	7.3	2.5	2.7
9	9.2	6.4	–1.1	1.9
10	8.7	5.9	1.9	1.8

[a/b]explanation provided within the text.

ΔHct_C = difference in CLM-III hematocrit pre-and post HD; ΔHct_P = difference in peripheral hematocrit pre-and post HD; ΔBV_{BVA} = change in absolute blood volume using BVA-100; $\Delta BV_{CLM\text{-}III}$ = change in relative blood volume using CLM-III; BV = blood volume; CLM-III = Crit-Line Model.

Peripheral Hct, CLM-III Hct and Hct_N

The range of pre-HD Hct_P was 30%–37%. Mean Hct_P (pre- and post-HD 31.6 ± 3.6 and 34.0 ± 4.5, respectively) was higher than the mean Hct_C (pre- and post-HD 29.9 ± 3.2 and 32.0 ± 4.2, respectively). Hct_N for each patient was higher than the post-HD Hct_P and Hct_C (range 29%–52%, mean 38.4 ± 6.2%). There was a poor correlation between Δ Hct_C and Δ Hct_P (post HD–pre HD Hct, R^2 –0.37; see Figure 2).

DISCUSSION

Our study is the first study in HD patients correlating intradialytic changes in absolute BV and RBV with DW during a single session of HD. BV analysis using BVA-100 has been used to measure total blood volume and assess the degree of volume overload or deficit in various non-dialysis settings. In a study by Katz et al.,[11] BVA was performed in 43 nonedematous patients with stable New York Heart Association class 2–4 congestive heart failure. The group with evidence of volume overload showed an increased risk of death or need for urgent cardiac transplantation. In the intensive care unit, BVA provided additional information to clinicians over and above pulmonary capillary wedge pressure-guided resuscitation resulting in a change in management in 44% of patients randomized to the BV group.[24]

It is well known that patients on maintenance HD tend to be volume-overloaded immediately before their dialysis treatment. The degree of volume-overload is dependent

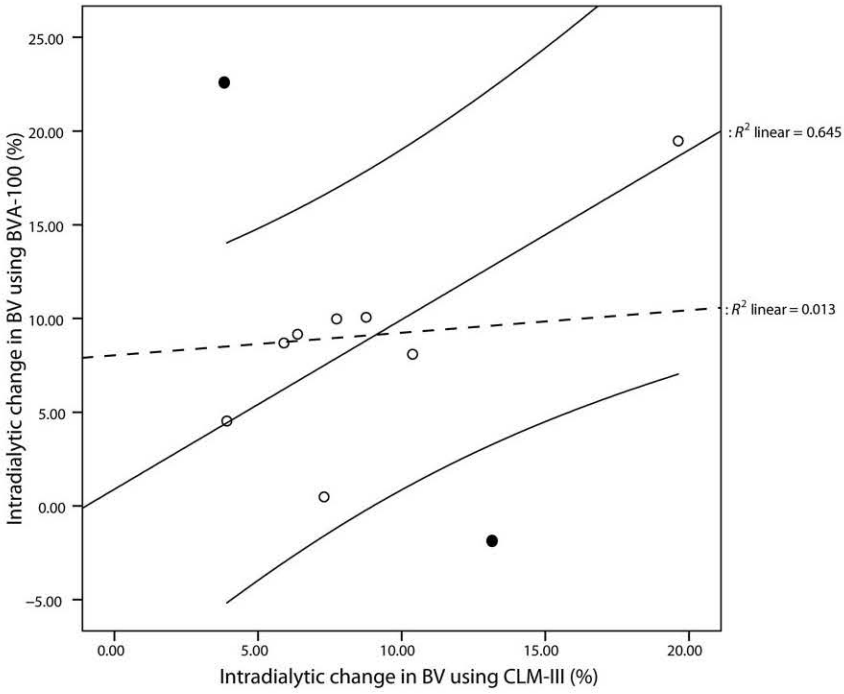

Figure 1 Spearman correlation graph.
Good correlation is seen between the BV change obtained using BVA and CLM-III in 8 out of 10 patients. This is represented using the central solid black line ($r^2 = 0.645$, $P < 0.05$). Dotted line represents correlation when all 10 patients are included ($r^2 = 0.013$). Peripheral solid lines indicate 2 standard deviation. BV = blood volume; BVA = blood volume analysis; CLM-III = Crit-Line Monitor.

upon salt intake in the interdialytic period as well as the adequacy of UF during each dialysis session. Our study highlights the marked heterogeneity in stable HD patients in terms of the degree of volume overload prior to initiation of dialysis, and more significantly, persistence of hypervolemia post dialysis despite prescribed UF.

A good correlation between the intradialytic change in RBV and absolute BV is seen in 8 of 10 patients (Figure 2). This result highlights a degree of concordance between the two methods of assessing BV changes during HD, keeping in mind that indicator dilution technique using radioisotopic tracer is the gold standard for accurate measurement of BV.[27] Although statistically there is a good correlation between the two modalities, in 5 out of 10 patients (excluding outlier patient 6) $\Delta BV_{CLM\text{-}III}$ was lower than the corresponding change ΔBV_{BVA}. This observation is consistent with a study by Dasselaar et al.[25] in which seven HD patients underwent simultaneous intradialytic radioimmunoassay-guided BV measurement and RBV measurement. Changes in RBV using Hct significantly underestimated changes in total BV. This was thought to be due to translocation of blood from the microcirculation to the macrocirculation, as evidenced by a rise in F-cell ratio (ratio of whole-body to systemic Hct) with dialysis. In 2 out of 10 patients (4 and 6) measurements from BVA-100 and CLM-III were not in agreement. Patient 4 had an increase in BV of 1.9% despite a 1.6-L fluid removal. Contrary to an expected decrease in Hct_P with volume expansion, his Hct increased by 2.8%, consistent with the intradialytic weight loss. This discrepancy in the results of the two techniques is difficult to explain. At the other end of the spectrum, Patient 6 had the smallest intradialytic change in Hct and RBV despite significant UF from the IV space. This is possibly due to the fact that at the time the second sample was drawn for Hct_P measurement, some refilling of IV space from EV-IS had already taken place. In summary, although CLM-III results correlated well, the device does not yield absolute values and does not indicate the degree of hypervolemia present.

In our study population, there were significant differences in patients' response to dialysis with respect to the recruitment of fluid from the EV space as compared to the IV space (UF_{IS}/UF_T, Table 2). This differential removal of fluid from various compartments highlights the difference

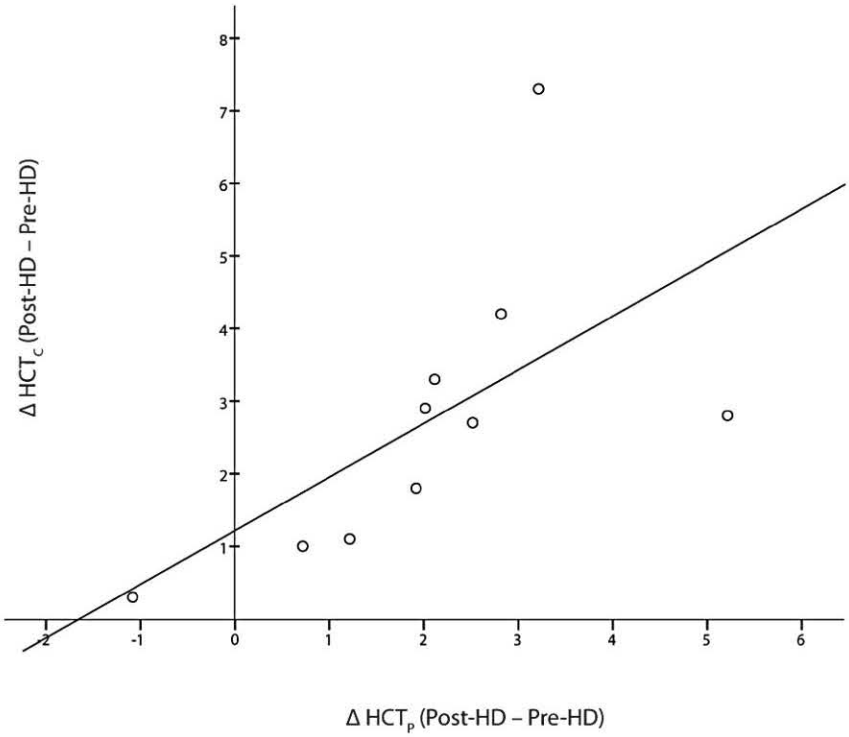

Figure 2 Spearman correlation graph.
X axis represents the difference between pre and post-HD Hct_P; Y axis represents the difference between pre and post-HD Hct_C (°, represents individual patients). Hct = hematocrit; HD = hemodialysis.

in individuals' capacity to refill and provides information not previously available in the management of HD patients. For example, patient 1 recruited a significant percentage (81%) of the UF_T from IS space while, at the other extreme patient 9 mobilized only 20% of fluid from the IS compartment, indicating that patient 9 either had a low refill capacity or the possibility that he was already volume contracted prior to initiation of HD and therefore did not have excess IS volume. The patients who demonstrate a lower refill capacity would likely be more prone to hemodynamic instability during HD and would potentially benefit from a change in their dialysis prescription if their individual refill capacity can be determined in the first few sessions of dialysis. Our study patients only had BV measurements performed during a single session of dialysis; perhaps serial measurements would be required to establish the true refill capacity of each patient. Also, the capacity to refill is affected by variation in characteristics of IS compartment of the body,[26] body posture at the time of dialysis and possibly serum albumin level. Our cohort of patients had relatively preserved pre-HD albumin levels which can possibly explain the preferential removal of fluid from the IS compartment noted in this group.

It is also evident that there is a disparity between the Hct_P and the Hct_N. This disparity may become important when a decision has to be made to titrate doses of erythropoiesis-stimulating agents (ESAs) in response to a low hemoglobin level.[13,28,29] Assuming that Hct_N represents the Hct in a state of euvolemia, knowledge of this value would help titrate doses of ESAs toward the target level and could lead to prescription of lower erythropoietin doses.

Several conclusions can be drawn from our study. First, BVA is useful to determine absolute BV and changes in BV. Second, fluid removal from EV and IS spaces can be calculated based on absolute BV changes to describe individual refilling ability. Third, Hct_N may prove to be a useful target for titration of ESAs. BVA-100 may prove useful in prescribing and monitoring UF rates and establishment of optimal BV and DW in HD patients. It should be noted, however, that the goal of dialysis should not be to treat a patient to normal BV in a single session. Once the patient's actual BV is known, and the patient is

hypervolemic, the BV can be safely treated by titrating the antihypertensive medications downward to increase the initial BP and then increasing UF. A state of normovolemia should be established stepwise and a follow-up BV performed within 1–4 months after the initial determination to verify that an optimum BV level has been reached.

Our study has several limitations. The absolute BV measurements were performed in a small number of patients, for a single session of HD only. Repeat measurements may be needed in order to establish the true ideal BV measurement, HctN and refill characteristics for each patient The normogram for ideal BV is derived from a healthy population and has been extrapolated to HD patients. Hence, further studies will be required in a larger number of HD patients to establish norms in this patient population as well as to assess the degree of correlation between various methods of BV assessment Third, the technique of BV measurement using RIA requires collaboration with a nuclear medicine facility and may not be feasible for isolated outpatient dialysis centers.

The BVA technique, providing measurement of absolute values for, and variation from, ideal volumes may prove useful in prescribing and monitoring UF rates and establishment of optimal BV and DW in HD patients. More accurate prescription of UF and DW has the potential to reduce the morbidity and mortality associated with chronic HD.

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