Determination of Circulating Blood Volume by Continuously Monitoring Hematocrit During Hemodialysis 1,2

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ABSTRACT

Dialysis-induced hypovolemia occurs because the rate of extracorporeal ultrafiltration exceeds the rate of refilling of the blood compartment. The purpose of this study was to evaluate a method for calculating circulating blood volume (BV) during hemodialysis (HD) from changes in hematocrit (Hct) shortly (2 to 10 min) before and after ultrafiltration (UF) was abruptly stopped. Hct was monitored continuously during 93 HD treatment sessions in 16 patients by an optical technique and at selected times by centrifugation of blood samples. Total plasma protein and albumin concentrations were also measured at selected times. Continuously monitored Hct correlated with Hct determined by centrifugation (R = 0.89, N = 579). Relative changes in BV determined by continuously monitored Hct were not different from those determined by total plasma protein concentration (P = 0.05; N = 273). Calculated BV at the start of dialysis (4.1 ± 1.3 L) was not different (P = 0.18, N = 12) from that derived anthropometrically from the patient's dry weight (4.6 ± 0.8 L), and calculated BV when UF was stopped was 3.2 ± 0.5 L (46 ± 7 ml/kg body wt). These latter estimates of BV are consistent with those determined previously by dilution techniques in HD patients. It was concluded that (1) relative changes in BV assessed by continuously monitored Hct were unbiased and (2) BV can be determined noninvasively during HD by continuously monitoring Hct and temporarily stopping UF.

Key Words: Blood volume, hematocrit, hemodialysis, monitor

Despite the ability of commercial hemodialysis machines to accurately remove fluid at a given desired rate, intradialytic hypovolemia and hypotension routinely occur because of an imbalance between the rate of extracorporeal ultrafiltration and the rate of refilling of the blood compartment (1). Previous work has shown that the refilling rate is patient specific and depends on both Starling forces within the blood compartment (2,3) and the hydration status of interstitial tissue (4). To assist in the prevention of intradialytic hypotension, several devices have been recently developed to monitor changes in blood volume during hemodialysis (5–9). These devices monitor either hematocrit (Hct) (usually by assessing blood hemoglobin concentration) or plasma protein concentration, therefore permitting the calculation of relative changes in blood volume (BV) on the basis of the principle of mass conservation. This approach is attractive because it can be adapted for continuous noninvasive monitoring; however, it can only determine relative changes in, but not absolute values of, circulating BV.

Schallenberg et al. (10) proposed that absolute circulating BV could be determined from relative changes in BV (assessed by blood hemoglobin concentration) before and after ultrafiltration (UF) was temporarily stopped. They derived an equation for calculating circulating BV but reported results for only one patient. The calculated values of circulating BV were variable and less than expected on the basis of the patient's body weight; thus, these investigators concluded that hemoglobin is likely distributed unevenly in the intravascular space. The purpose of this study was to evaluate the method of Schallenberg et al. (10) for calculating circulating BV during multiple clinical hemodialysis sessions from changes in Hct shortly before and after abruptly stopping UF. We found that calculated values of circulating BV were reasonable and consistent with those previously reported by the use of other methods.

METHODS

Experimental

Sixteen (5 male and 11 female) patients at the University of Utah–affiliated Bonneville Dialysis Unit (Ogden, UT) were enrolled in this study after giving informed consent. Each patient was studied on six separate occasions for a total of 93 treatment sessions. (One patient missed two sessions because he received a renal transplant, and one patient missed one session because she had a clotted vascular access.)
Patients were treated by routine dialysis with minimal intervention by the research staff. Hemodialysis was performed with 2008E machines (Fresenius, Concord, CA), bicarbonate dialysate, and cellulose acetate membrane hollow-fiber dialyzers (CA series; Baxter Healthcare, Round Lake, IL). The dialysate flow rate was fixed at 500 ml/min, but the blood flow rate and treatment time were prescribed individually for each patient by the use of urea kinetics. The UF rate (UFR) ranged between 457 and 1,971 ml/h and was selected by the dialysis staff to remove sufficient fluid to achieve the patient's prescribed dry weight. The predetermined UFR was held constant during each session, except when it was necessary to change the rate because of intradialytic symptoms. The dialysate sodium concentration was programmed to vary linearly from 150 mEq/L at the start to 142 mEq/L at the end of dialysis for all sessions.

Hct was monitored noninvasively and continuously with the CRIT-LINE instrument (In-Line Diagnostics, Riverdale, UT) during each session, as described (8). Before hemodialysis, a sterile, plastic, disposable blood chamber (Beta prototype; In-Line Diagnostics) was placed in the blood circuit between the arterial blood tubing and the dialyzer. The CRIT-LINE instrument uses a transmissive photometric technique to determine the Hct on the basis of both the absorption properties of hemoglobin and the scattering properties of red blood cells passing through the blood chamber. The tubing set, disposable blood chamber, and blood compartment of the dialyzer were then rinsed and primed with normal saline. Although dialyzers were reused, the blood tubing and blood chamber were not. Blood samples were taken before hemodialysis, hourly during the session, and immediately before stopping hemodialysis for determining Hct by microcentrifugation and total plasma protein and albumin concentrations. During one session on each patient, blood samples were also taken every 15 min for determining Hct by microcentrifugation.

Calculations

The relative change in blood volume (ΔBV) was calculated from the observed change in Hct by use of the following equation

$$\Delta BV = \frac{BV}{BV(0)} - 1 = \frac{H(0)}{H} - 1 \quad (\text{Equation 1})$$

The values of Hct and BV at the start of hemodialysis are denoted as H(0) and BV(0), respectively; in this and subsequent equations, Hct is denoted as H. Although H and ΔBV can be determined at any time during hemodialysis, absolute values of circulating BV, i.e., BV and BV(0), cannot. H and ΔBV were recorded and calculated, respectively, by the CRIT-LINE instrument every 10 s during hemodialysis. Hct values are expressed as a percentage of total BV; the units are implied and not specifically indicated.

Assuming that changes in BV during hemodialysis occur only because of extracorporeal UF and vascular refilling, BV will decrease when the UFR exceeds the vascular refilling rate. Conversely, BV will increase as the result of vascular refilling when UF is stopped temporarily during hemodialysis. Suppose that UF is abruptly stopped at a certain time, denoted by τ, during hemodialysis. Shortly before τ, BV will be decreasing, and shortly after τ, BV will be increasing. If it is assumed that the vascular refilling rate is identical shortly before and after τ, before the body has time to adjust, an equation can be derived (see Appendix) for calculating circulating BV at the start of dialysis, BV(0)

$$BV(0) = \frac{UFR}{d(BV)} \frac{d(BV)}{dt} (\tau -) - \frac{d(BV)}{dt} (\tau +) \quad (\text{Equation 2})$$

where τ− and τ+ denote the times shortly before and after, respectively, UF is stopped. Circulating BV at the time UF is stopped, BV(τ), can also be calculated by an analogous equation. We found it most convenient to calculate this latter parameter directly from changes in Hct (see Appendix) as

$$BV(\tau) = \frac{H(\tau)}{UF} \frac{dH}{dt} (\tau -) - \frac{dH}{dt} (\tau +) \quad (\text{Equation 3})$$

Equations 2 and 3 demonstrate that it is possible to calculate circulating BV during hemodialysis when UF is temporarily stopped by determining the rate of change (d/dt) of Hct (or BV) shortly before and after stopping UF. It should be emphasized that these relationships are not valid when other interventions (e.g., saline infusion, use of the Trendelenburg position), in addition to stopping UF, are also performed because they will alter Hct and BV (10.11).

Both hematocrit-time and ΔBV-time profiles were plotted for each treatment session. From the ΔBV-time profile, circulating BV at the start of hemodialysis was calculated by the use of Equation 2, and from the Hct-time profile, circulating BV at the time UF was stopped was calculated by the use of Equation 3. The derivatives in Equations 2 and 3 were determined by drawing a straight line visually through the profiles 2 to 10 min before and after UF was stopped (see Figure 3B below).

Analytical

Total plasma protein and albumin concentrations were determined with an automated analyzer (SYNCHRONE CX-5 & CX-7; Beckman, Brea, CA). Intra-assay precision for total plasma protein determinations of 0.3 g/dL (standard deviation) was reported by the manufacturer.

Statistics

Linear regression was performed with Lotus 1-2-3 Release 4 software (Cambridge, MA). All values are reported as the mean ± the standard deviation. Analyses with P < 0.01 were considered significant.

RESULTS

Although determinations of Hct by the CRIT-LINE instrument correlated well with those determined by centrifugation (Figure 1), the slope (1.31 ± 0.03) was not equal to 1 (P < 0.001). By the use of a nested analysis of variance statistical model (12), it was shown that discrepancies between Hct estimates were larger between different treatment sessions than within sessions (P < 0.001). The standard deviation of the difference in Hct estimates within treatment sessions was 1.6, whereas that between sessions was 2.4. This analysis suggests that the CRIT-LINE instrument was able to detect relative changes in Hct within an individual treatment session better than that implied from the results shown in Figure 1.
Relative changes in BV determined by the CRIT-LINE instrument also correlated well with those determined by total plasma protein concentration (Figure 2). Although there is considerable scatter in this plot, there was no difference (0.9 ± 6.0%; P = 0.05) between these two estimates of ΔBV when they were compared with a paired t test. This analysis implies that ΔBV determined by the CRIT-LINE instrument and by total plasma protein concentration give indistinguishable results. Relative changes in BV determined by the CRIT-LINE instrument also correlated well with those determined by albumin concentration (R = 0.64, N = 261; graph not shown).

Figures 3A and B show examples of relative changes in BV determined by the CRIT-LINE instrument during treatment sessions on different patients. In the example shown in Figure 3A, the decrease in BV was most rapid at the beginning of treatment. The shape of this ΔBV-time profile is similar to that predicted by mathematical models previously described (2,3). Profiles of this shape were not common in this study, however. A more typical profile is shown in Figure 3B, where relative changes in BV were minimal at the beginning of treatment but where BV decreased substantially later in the session. In this example, UF was stopped temporarily when this patient experienced muscle cramps. The method for determining dΔBV/dt(τ−) and dΔBV/dt(τ+) is also shown on this figure.

Circulating BV was determined when UF was stopped during 32 treatment sessions on 12 patients who suffered intradialytic morbidity such as hypotension, muscle cramps, or lightheadedness and no additional interventions besides stopping UF were performed. Figure 4 shows the average values of
or plasma protein concentrations (5–9). When using Hct to assess relative changes in BV, it is assumed that there are no changes in red blood cell volume during hemodialysis. Previous work has suggested that changes in red blood cell volume during hemodialysis are indeed small despite changes in plasma sodium concentration and plasma osmolality (14–16). In this study, Hct determined by the CRIT-LINE instrument correlated well with those determined by centrifugation but not as well as with those determined by this instrument in vitro (R = 0.996) (8). Our statistical analysis demonstrated that some of the differences between the Hct determined by the CRITLINE instrument and that determined by centrifugation occurred between treatment sessions and could be ascribed to additional variability associated with the disposable blood chambers or, possibly, with centrifugal determinations of Hct.

The good correlation between relative changes in BV assessed by the CRIT-LINE instrument and those assessed by total plasma protein concentration (and albumin concentration) demonstrates that these approaches produce similar results. Although there is considerable scatter between these estimates of relative change in BV (Figure 2), it should be noted that the standard deviation between these estimates (6.0%) is comparable to that for determinations of total plasma protein concentration by the automated analyzer. Therefore, we can only conclude that relative changes in BV assessed by the CRIT-LINE instrument are unbiased and at least as accurate as those assessed by changes in total plasma protein concentration measured by the use of routine clinical assays.

The temporal profile of relative changes in BV determined in this study were highly variable, and this variability likely reflects patient-specific characteristics in response to the acute removal of large amounts of fluid from the blood compartment during hemodialysis. Previous mathematical models of body fluid kinetics during hemodialysis have suggested that BV should decrease most rapidly at the beginning of therapy (2,3). The results from this study did not confirm those predictions. This lack of agreement between theory and experimental results suggests that factors other than those included in previous mathematical models, such as the variable dialysate sodium concentration used, the hydration status of interstitial tissue (4) and physiologic responses affecting the heart and peripheral circulation (17,18), are likely important in governing changes in BV during hemodialysis.

Schneditz et al. (3) have recently calculated values of absolute BV in hemodialysis patients by comparing relative changes in BV in response to a short pulse of UF during the first hour of hemodialysis with that predicted by a mathematical model. These calculated values of BV correlated well with those calculated from anthropometry. We used a different approach in this study to estimate circulating BV because the shape of most ΔBV-time profiles did not correspond to those...
predicted from previous mathematical models. This approach for estimating circulating BV is similar to that previously attempted on a single patient by Schallenberg et al. (10) and is model independent, relying instead on the assumption that the vascular refilling rate is not significantly altered over several minutes when UF is stopped. Although this assumption has not yet been experimentally validated, it appears reasonable and there is no experimental evidence to the contrary. These results on 12 patients are more favorable than those reported previously and suggest that this approach may provide a method for noninvasively determining circulating BV in hemodialysis patients. We were unable to demonstrate a significant difference between circulating BV at the start of hemodialysis and those calculated from the patient’s dry weight by anthropometry. This result was not different if either the patient’s predialysis body weight or the patient’s lean body mass (as calculated from both height and weight [13]) were instead used as the basis for calculating circulating BV (data not shown).

The values of circulating BV reported in this study can also be compared with values of BV previously determined in hemodialysis patients by the dilution techniques of Kim et al. (19). These investigators determined BV before the start of hemodialysis in three groups of patients and calculated mean BV of 3.817, 4.429, and 4.058 L. Moreover, they reported that BV less than 2.8 L (50 mL/kg body wt) were associated with intradialytic hypotension. Our estimates of circulating BV are consistent with those previous results.

Although detailed physiologic responses to volume reduction were not considered in this study, we have recently reported that relative changes in BV correlated with the amount of fluid removed during hemodialysis and that intradialytic morbidity events occurred when the Hct reached a patient-specific threshold (20). The latter observation implies that intradialytic morbidity events occurred when the absolute circulating BV decreased to a critical value. The capability of determining absolute circulating BV by the technique described in this study would allow this concept to be applied even when the red blood cell mass changes over time. This and other potential clinical applications of absolute circulating BV measurements, however, need further validation.

We conclude that relative changes in BV assessed by continuously monitored Hct were unbiased and that circulating BV during hemodialysis calculated by changes in continuously monitored Hct before and after temporarily stopping UF were not different from anthropometric estimates and were similar to those previously determined by dilution techniques.

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APPENDIX

Although Equation 2 was derived previously by Schallenberg et al. (10), an alternative derivation is shown here to clarify present terminology. Changes in circulating BV with time (d(BV)/dt) during hemodialysis are dependent on the UFR and the vascular refilling rate (VRR) according to the following equation

\[
\frac{d(BV)}{dt} = UFR - VRR \quad \text{(Equation 1A)}
\]

Suppose that at time \(\tau\), UF is stopped abruptly during hemodialysis. Shortly before UF is stopped, the circulating BV will decrease according to Equation 1A, or

\[
\frac{d(BV)}{dt} (\tau^-) = UFR - VRR \quad \text{(Equation 2A)}
\]

where \(\tau^-\) denotes the time shortly before UF is stopped. Shortly after stopping UF, circulating BV will increase according to Equation 1A with UFR set equal to zero, or

\[
\frac{d(BV)}{dt} (\tau^+) = VRR \quad \text{(Equation 3A)}
\]

where \(\tau^+\) denotes the time shortly after UF is stopped. The relationship between changes in circulating BV and changes in \(\Delta BV\) is (see Equation 1 in the Text)

\[
\frac{d(BV)}{dt} = BV(0) \frac{d(\Delta BV)}{dt} \quad \text{(Equation 4A)}
\]

where BV(0) is the value of circulating BV at the beginning of hemodialysis. Assuming that the VRR is identical shortly before and after UF is stopped. VRR can be eliminated from Equations 2A and 3A and the result for BV(0) can be solved using Equation 4A as

\[
BV(0) = \frac{UFR}{\frac{d(\Delta BV)}{dt} (\tau^+) - \frac{d(\Delta BV)}{dt} (\tau^-)} \quad \text{(Equation 5A)}
\]

This is Equation 2 in the Text.

The relationship between changes in \(\Delta BV\) and changes in Hct (H) is (see Equation 1 in the Text)

\[
\frac{d(\Delta BV)}{dt} = - \frac{H(0) dH}{dt} \quad \text{(Equation 6A)}
\]

Substituting Equation 6A into Equation 5A and using Equation 1 in the Text yields an equation for circulating BV at the time UF is stopped

\[
BV(\tau) = \frac{H(\tau) UFR}{\frac{dH}{dt} (\tau^-) - \frac{dH}{dt} (\tau^+)} \quad \text{(Equation 7A)}
\]

This is Equation 3 in the Text.
REFERENCES


