Hematocrit (H) levels can change during hemodialysis, and these changes in H are inversely related to changes in blood volume (BV). The objectives of this study were to determine whether mean arterial pressure (MAP) decreases with decreasing BV and rising H during hemodialysis, and to determine the relationship between dialysis induced intravascular volume depletion and intradialytic morbidity events (IME), defined as hypotension, cramping, or lightheadedness that led to dialysis staff intervention. We monitored H continuously using a noninvasive optical technique in 93 hemodialysis sessions in 16 patients. IME occurred in 48 sessions. MAP decreased with increasing H in 10 of 16 patients (P < 0.05), but the relationship between MAP and H varied among the patients. The rate of BV change during sessions without morbidity (5.6 ± 3.6 [SD] %/hr) was lower (P < 0.001) than that preceding IME in the other sessions (12.2 ± 5.5 [SD] %/hr). Twelve of 16 patients who exhibited recurrent IME during this study experienced these events when H reached a patient specific threshold. It is concluded that MAP decreases with decreasing BV and increasing H in many patients on hemodialysis, and that a high rate of BV change often indicates that IME are forthcoming. It is further hypothesized that a patient specific H threshold is indicative of a critical BV level below which certain patients experience IME.

Methods

Treatment of patients in end-stage renal failure by hemodialysis is frequently accompanied by acute symptoms or complications, such as hypotension, severe muscle cramps, and lightheadedness. Although the pathophysiology of these intradialytic morbidity events (IME) is complex and multifactorial, hypovolemia likely plays a role in triggering many IME.

Intravascular volume depletion results from an imbalance between the rates of extracorporeal ultrafiltration and refilling of the blood compartment. Because red cell volume remains essentially constant during hemodialysis, changes in hematocrit are inversely related to changes in circulating blood volume (BV). This relationship has been used in attempts to predict dialysis induced hypotension. For example, Maeda et al. studied the relationship between changes in BV (assessed by changes in hematocrit) and dialysis induced hypotension in 29 hypotension prone patients on hemodialysis. These investigators found no relationship between intradialytic intravascular volume depletion and acute onset of hypotension. In contrast, de Vries et al. divided 37 patients on hemodialysis into groups according to their predialysis hydration status and demonstrated that the change in blood volume (ΔBV) by the end of dialysis, and the number of hypotensive events, were greater in the dehydrated patients than in either the normohydrated or overhydrated patients. Moreover, ΔBV normalized by the ultrafiltration volume was significantly greater immediately preceding the hypotensive episode than in uneventful hemodialysis sessions. These two previous studies yielded conflicting results and did not address IME other than hypotension that might also be related to intravascular volume depletion. The main objective of the current study was to determine the relationship between dialysis induced intravascular volume depletion and IME.

Experimental

Sixteen (5 men and 11 women) patients at the University of Utah affiliated Bonneville Dialysis Unit (Ogden, UT) were enrolled in this study after giving informed consent. Study patients were selected by the dialysis staff as either generally stable (eight patients) or hypotensive prone (eight patients), based on previous clinical experience. These two groups of patients were chosen to ensure that some dialysis sessions would be uneventful and some would contain IME. The results from these two groups were not, however, compared to each other. Each patient was studied on 6 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 clot-
ted vascular access.) The six sessions on each patient were conducted within a period of 4 weeks when the erythropoietin dose remained constant.

Patients were treated by routine dialysis with minimal intervention by the research staff. Hemodialysis was performed using 2008E machines (Fresenius, Concord, CA), bicarbonate dialysate, and cellulose acetate membrane hollow fiber dialyzers (CA series; Baxter Healthcare, Round Lake, IL). Dialysate flow rate was fixed at 500 ml/min, but blood flow rate and treatment time were prescribed individually for each patient using urea kinetics to ensure a delivered urea Kt/V of 1.2 or greater. The ultrafiltration rate ranged between 457 and 1971 ml/hr and was selected by the dialysis staff to remove sufficient fluid to achieve the patients’ prescribed dry weight. The predetermined ultrafiltration rate was held constant during the session, except when it was necessary to change the rate because of IME. The dialysate sodium concentration was programmed to vary from 150 mEq/l at the start to 125 mEq/l at the end of dialysis. Body weight was determined by standing scale before and after each session. Blood pressure and pulse rate were monitored by automated cuff measurement every 15 min throughout hemodialysis.

Hemocrit was monitored noninvasively and continuously with the Crit-Line instrument (In-Line Diagnostics, Riverdale, UT) during each session, as described. 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 hematocrit based on 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 chambers were not. Blood samples were taken before hemodialysis, hourly during the session, and immediately after hemodialysis for determining hematocrit by microcentrifugation, plasma osmolality, and sodium and calcium concentrations. During one session in each patient, blood samples were also taken every 15 min for additional measurements of hematocrit by microcentrifugation.

Calculations

The change in blood volume (ΔBV) was calculated from the observed change in hematocrit (H) using the following equation:

\[
\Delta BV = \frac{BV - BV_i}{BV_i} = \frac{H}{H_i} - 1
\]

(1)

The subscript \(i\) denotes the parameter value at the start of hemodialysis. The parameters \(H\) and \(\Delta BV\) are time dependent and can be determined at any time during hemodialysis. \(H\) and \(\Delta BV\) were recorded and calculated by the Crit-Line instrument every 10 sec during hemodialysis. Hematocrit values are expressed as a percentage of total blood volume; the units are implied and not specifically indicated.

A ΔBV time profile was plotted for each treatment session, and the maximum ΔBV (ΔBV\text{max}) was recorded. The rate of change of ΔBV (ΔBV/Δt) occurring in the hour preceding the IME (or before the end of the treatment when no IME occurred) was also determined for each session. Furthermore, circulating BV at the time when an IME occurred was estimated (only when no additional resuscitational efforts besides temporarily stopping extracorporeal ultrafiltration were necessary) using the method described elsewhere.

Analytic

Plasma sodium and calcium concentrations were determined using an autoanalyzer (Béckman CX-5 and CX-7, Brea, CA). Plasma osmolality was measured using a commercial instrument (Wescor 5500, Logan, UT). Hematocrit determinations by the Crit-Line instrument correlated well with those determined by centrifugation (R = 0.89, N = 579); the standard deviation of H determinations was estimated as 2.4.

Intradialytic Morbid Events

For the purposes of the current study, hypovolemic morbidity was defined as the occurrence of one or more of the following events leading to dialysis staff intervention and the interruption of ultrafiltration: 1) hypotension defined as mean arterial pressure (MAP) < 75 mm Hg, 2) cramping, or 3) lightheadedness. The two latter symptoms were included in the definition because they are frequently associated with rapid fluid removal and hypotension during hemodialysis. Continuous hematocrit was plotted versus time for each patient during all treatment sessions, and IME were contemporaneously noted in relation to the hematocrit.

Data Analysis and Statistics

The data for each session were grouped according to whether any IME occurred. All results were summarized as the mean ± SD. The significance of differences between sessions with and without IME was determined using an unpaired Student’s t-test. The significance of differences between values at the start and end of hemodialysis was determined using a paired Student’s t-test. Linear regression was performed using Lotus 1-2-3 Release 4 software (Lotus, Cambridge, MA).

Results

Changes in Plasma Chemistry during Hemodialysis

IME occurred in 52% (48/93) of hemodialysis sessions (Table 1). Hypotension occurred in 22, muscle cramps without hypotension in 14, and lightheadedness without hypotension or muscle cramps in 12 sessions. Plasma osmolality and sodium concentration can influence blood volume by inducing fluid shifts between body compartments, whereas plasma calcium may affect blood pressure by modulating cardiac contractility and vascular tone. Plasma osmolality decreased (\(P < 0.001\)) from 308 ± 11 mOsm/kg H₂O at
Table 1. Comparison of Ultrafiltration Rate, Ultrafiltration Volume Normalized by Patient Body Weight, Maximum Changes in Blood Volume, and the Rate of Change in ∆BV During Hemodialysis Sessions with or without Intradialytic Morbid Events

<table>
<thead>
<tr>
<th></th>
<th>With IME</th>
<th>Without IME</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of sessions</td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td>UFR (ml/hr)</td>
<td>1250 ± 300*</td>
<td>950 ± 220*</td>
</tr>
<tr>
<td>Normalized UFV (ml/kg)</td>
<td>58.0 ± 17.0*</td>
<td>46.2 ± 13.9*</td>
</tr>
<tr>
<td>∆BVmax (%)</td>
<td>-18.1 ± 7.6</td>
<td>-14.5 ± 6.7</td>
</tr>
<tr>
<td>Correlation coefficient for regressions of ∆BVmax (%) on normalized UFV (ml/kg)</td>
<td>-0.04*</td>
<td>-0.52*</td>
</tr>
<tr>
<td>∆BV/Δt (%) (ml/hr)</td>
<td>12.2 ± 5.5*</td>
<td>5.6 ± 3.6*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
* Values for hemodialysis sessions with and without IME are different (P < 0.001).

Table 1 summarizes the ultrafiltration rates, ultrafiltration volumes, and changes in blood volume for sessions with and without IME. Ultrafiltration rates in sessions with IME were higher (P < 0.001) than those in sessions without intradialytic morbidity; however, ∆BVmax was no different between the two groups. There was no correlation between ∆BVmax and normalized ultrafiltration volume in sessions with IME, but there was a significant correlation between ∆BVmax and normalized ultrafiltration volume in sessions without IME. The rate of ∆BV change (∆BV/Δt) for sessions with no morbidity (5.6 ± 3.6 %/hr) was lower (P < 0.001) than that for sessions with IME (12.2 ± 5.5 %/hr). Only 1 of 45 sessions without IME exhibited a ∆BV/Δt as high as 12 %/hr at any time (observed during the first half hour) during treatment.

Mean Arterial Pressure Versus Hematocrit

The dependence of blood pressure on continuous hematocrit was variable, both from day to day and from patient to patient. Figure 1A shows the results from an example hemodialysis session where both MAP and ∆BV decreased with time. Figure 1B shows the correlation of MAP versus hematocrit determined for this patient using time synchronized hematocrit values from all six treatment sessions. Inverse correlations (r = −0.28 to r = −0.81, P < 0.05) between MAP and hematocrit were observed for 10 of the 16 patients. Figure 2A provides example results from one of the patients in whom MAP remained essentially stable in spite of decreasing ∆BV. Figure 2B displays the lack of correlation of MAP versus hematocrit from all six treatment sessions for this patient.

Hematocrit Threshold at IME

Thirteen of the 16 patients experienced at least 1 IME during the 6 studied hemodialysis sessions. Table 2 summarizes the hematocrit levels when IME occurred. (One patient had only one treatment when IME occurred; this result was omitted here.) Note that the number of IME in Table 2 exceeds 48 because there were multiple IME in some treatment sessions. Because the hematocrit at the time the IME occurred during the six treatment sessions in a given patient appeared to be consistent, these values were averaged and the mean value was termed the hematocrit threshold. For all 12 patients who had multiple IME, the mean standard deviation of the observed hematocrit threshold was 1.4. This implies that
the hematocrit threshold remained relatively constant in a given subject. Figure 3 shows an example of this concept. In these figures, hematocrit is plotted versus time during two treatment sessions on the same patient. Note that IME occurred near the hematocrit threshold for this patient. The hematocrit in sessions without IME often approached, but rarely exceeded, the hematocrit threshold.

Estimation of circulating BV was possible when ultrafiltration was stopped abruptly (with no additional resuscitation efforts performed), allowing BV to recover by refilling from the extravascular space.9 Any other intervention (e.g., saline infusion, use of the Trendelenburg position) would likely alter the shape of the ΔBV time profile, making it difficult to estimate accurately circulating blood volume. Using this method, circulating BV at the hematocrit threshold was estimated to be 46 ± 7 ml/kg (N = 32).

Discussion

Approximately one third of all hemodialysis treatment sessions are complicated by acute symptoms, with hypotension being the most frequent one reported.2 Although osmolar imbalance,3,9 inappropriate neurohumoral responses,14,15 and changes in body temperature16 appear to be important contributing factors influencing dialysis induced hypotension,17 hypovolemia likely acts as a common trigger or end result of these abnormalities. Muscle cramping is the second

Table 2. Hematocrit Threshold Determined by the Crit-Line Instrument When Intradialytic Morbid Events Occurred

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>No. of IME*</th>
<th>H Threshold (mean ± SD)</th>
<th>Mean H Change Before IME from Start of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>40 ± 1.6</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>38 ± 1.3</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>31 ± 2.7</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>46 ± 1.9</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>44 ± 0.5</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>38 ± 2.2</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>44 ± 0.5</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>40 ± 1.2</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>38 ± 0.4</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>49 ± 0.9</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>36 ± 0.5</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>49 ± 2.2</td>
<td>9</td>
</tr>
</tbody>
</table>

* Total number of IME occurring during the six study sessions for each patient.
most common acute complication of hemodialysis, and hypovolemia has also been implicated as a causal factor in its occurrence.

In the current study, IME occurred in more than 50% of hemodialysis treatment sessions. Hypotension occurred in 24%, muscle cramps without hypotension in 15%, and lightheadedness without either hypotension or muscle cramps in 13% of these sessions. These rates of occurrence are similar to those reported in some previous studies. The relatively high incidence of hypotension reported here likely reflects bias in selecting some patients who are prone to development of symptoms. Intradialytic morbidity occurred in the current study more frequently in sessions with higher ultrafiltration rates, as expected.

The results from this study confirm that blood pressure declines during hemodialysis therapy in many patients and that these decreases in blood pressure are related to decreases in BV as assessed by increases in hematocrit. These results are also consistent with the recent findings of Lins et al., who demonstrated a correlation between changes in systolic blood pressure and changes in plasma volume as measured by dilutional techniques during hemodialysis.

Establishing a method for predicting IME related to hypovolemia before the symptoms actually occur would be useful for clinical dialysis. In the search for such a predictor of dialysis induced hypovolemic morbidity, obvious consideration was given to the magnitude of BV changes (i.e., ABVmax). Our results (Table 1) and those of others do not support such a relationship, however. One patient may experience hypotension after only a 5% decrease in BV, whereas another is able to maintain blood pressure with a 20% decrease in BV. These differences may be caused, in part, by differences in the patients' initial state of hydration and neurohumoral compensatory responses.

The second consideration was the rate of decrease in BV immediately before IME. In support of this hypothesis, de Vries et al. have demonstrated that BV decreases more rapidly before hypotensive events than in hemodialysis sessions without hypotension. Our results (Table 1) are similar to those findings of de Vries et al. Presumably, a rapid decrease in BV does not allow sufficient time for optimal compensatory neurohumoral responses to develop to support the blood pressure. Although the rate of decrease in BV identified an increased probability of IME, such a decrease indicates only that IME are forthcoming, and does not help to predict when they will occur. Others have not observed large decreases in BV before all hypotensive events.

The third possibility was that a patient specific, critical BV exists that triggers IME, as suggested more than two decades ago by Kim et al. In that study, approximately 80% of all hypotensive events occurred when the patients' absolute BV, as determined by dilutional techniques, was below 2800 ml (or 50 ml/kg). In the current study, the estimated BV at the hematocrit threshold was 46±7 ml/kg and similar to that determined by Kim et al. Furthermore, the consistency of the hematocrit threshold for IME (Table 2) supports the hypothesis that critical BV exist for certain patients that can be determined during hemodialysis by continuously monitoring the hematocrit.

The hematocrit threshold concept for IME prediction appears to be valid for some of the patients in this study, although the patients did not always manifest IME when the hematocrit threshold was reached, presumably because neurohumoral responses were inadequate to compensate for the decrease in BV. The potential usefulness of this concept is that after establishing a hematocrit threshold by repeated determinations on a given patient, hypovolemia induced morbidity potentially can be prevented during subsequent dialysis treatments if ultrafiltration is tailored to avoid exceeding the hematocrit threshold. A major practical concern will be whether the threshold value can be determined with sufficient consistency. Stated in other words, it will be necessary for the standard deviation of the hematocrit threshold to be small relative to the typical change in hematocrit during the treatment for this approach to be clinically useful. An additional concern with this concept relates to the consistency of the hematocrit threshold with changing conditions in the patient on dialysis. For example, red cell mass, and therefore the hematocrit threshold, may change secondary to erythropoietin therapy or bleeding. This important issue will need to be addressed in ensuing studies. Additional studies will also be necessary to verify that altering therapy based on the hematocrit threshold can indeed reduce intradialytic morbidity and enhance the efficiency of fluid removal during hemodialysis. For example, hematocrit and blood volume monitoring could serve as a basis for ultrafiltration profiling; thus, fluid removal could be maximized when intravascular volume is high and decreased when intravascular volume is low before hypotension and its associated symptoms actually occur. The hematocrit threshold concept could also potentially help to more scientifically define dry weights for patients on hemodialysis.

In conclusion, these data demonstrate that MAP decreases with decreasing BV and increasing hematocrit in many patients on hemodialysis, and that a high rate of BV change indicates that IME are forthcoming. In addition, we hypothesize that a patient specific hematocrit threshold is indicative of a critical BV level below which certain patients experience IME.

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