Hypervolemia Is Associated With Increased Mortality Among Hemodialysis Patients

Rajiv Agarwal

Abstract—Among chronic hemodialysis patients, 217 hospitalizations per 1000 patient-years are attributed to congestive heart failure; some are attributable to unrecognized hypervolemia. Hypervolemia can be detected by relative plasma volume (RPV) monitoring. The purpose of this study was to examine among 308 patients on long-term hemodialysis the value of slope of RPV compared with either ultrafiltration (UF) volume or UF rate index in determining all-cause mortality. RPV slopes were calculated by least-squares regression. These slopes were related to all-cause mortality in unadjusted and adjusted Cox proportional hazards models. Over a median follow-up of 30 months (interquartile range: 14 to 54 months) 96 patients (31%) died, yielding a crude mortality rate of 113/1000 patient-years. We found the following: (1) RPV slope measurements were of prognostic significance (hazard ratio of flatter slopes [>1.39%/h]: 1.72; P=0.01); (2) the UF volume alone was not prognostically informative (hazard ratio of higher UF volume [>2.7 L of dialysis]: 0.78; P=0.23); (3) the UF rate index alone was also not prognostically informative (hazard ratio of higher UF rate index [>8.4 mL/kg per hour]: 0.89; P=0.6); and (4) the prognostic relationship of RPV slope to mortality was independent of conventional and unconventional cardiovascular risk factors including the UF volume, UF rate, or UF volume per kilogram of postweight. RPV monitoring yields information that is prognostically important and independent of several risk factors including UF volume, aggressiveness of UF, and interdialytic ambulatory blood pressure. Its use to assess excess volume-related morbidity among chronic hemodialysis patients should be tested in randomized, controlled trials. (Hypertension. 2010;56:512-517.)

Key Words: dry weight ■ relative plasma volume monitoring ■ prognosis ■ end-stage renal disease ■ hypertension
UF rate per kilogram of postdialysis weight in determining all-cause mortality.

Methods

Participants

Patients ≥18 years of age who had been on chronic hemodialysis for >3 months and were free of vascular, infectious, or bleeding complications within 1 month of recruitment who were dialyzed 3 times a week at 1 of the 4 dialysis units in Indianapolis affiliated with Indiana University were enrolled in the study. Those who missed ≥2 hemodialysis treatments over 1 month, abused drugs, or had chronic atrial fibrillation or body mass index of ≥40 kg/m² were excluded. Patients who had a change in dry weight or antihypertensive drugs within 2 weeks were also excluded. The study was approved by the institutional review board of Indiana University and the Roudebush Veterans’ Affairs Medical Center Research and Development Committee in Indianapolis, and all of the subjects gave written informed consent.

Measurements

RPV Monitoring

RPV monitoring was performed on a single occasion with Crit-Line III-TQA, which is a clinically available device that incorporates photo-optical technology to noninvasively measure absolute hematocrit (Hemamecet).18 Hematocrit was measured every 20 seconds throughout the duration of hemodialysis. Measurements made by the machine have been validated against hematocrits measured by centrifugation.14 We exported the machine stored time and hematocrit data to a relational database for additional analysis.

Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure (BP) monitoring was performed after either the first or midweek hemodialysis session for 44 hours. Most recordings were performed after the RPV monitoring. However, when this was not possible, then ambulatory BP monitoring was performed within 2 weeks of RPV monitoring. Ambulatory BP was recorded every 20 minutes during the day (6:00 AM to 10:00 PM) and every 30 minutes during the night (10:00 PM to 6:00 AM) using a SpaceLabs 90207 ambulatory BP monitor (SpaceLabs Medical Inc) in the nonaccess arm, as reported previously.19 Hourly averages were calculated. The mean of hourly average values represents the 44-hour mean systolic or diastolic BP.

Outcomes

All-cause mortality was the primary focus of our study, and this outcome was available in every patient. Patients were censored on the date that they had the last dialysis visit if they were transplanted or left the dialysis unit.

Data Analysis

The change in plasma volume with UF approximates a first-order elimination kinetics during hemodialysis. For each patient, RPV slope was calculated using least-squares linear regression as follows. First, we calculated the fraction of blood free of hematocrit using the formula 100 − percentage of hematocrit. Next, we took the natural log of this fraction as the dependent variable. The independent variable was time measured in hours elapsed since initiation of dialysis. The coefficient on the dialysis time term in this model was calculated using least-squares linear regression as follows.

\[
\frac{\frac{1}{\text{RPV}}}{\log(\text{hematocrit})} = \beta_1 + \beta_2 \times \text{time} + \epsilon
\]

where \(\beta_1\) and \(\beta_2\) are the coefficients on the intercept and time variable, respectively, and \(\epsilon\) is the error term. The coefficient on the dialysis time term in this model was variable was time measured in hours elapsed since initiation of dialysis kinetics during hemodialysis. For each patient, RPV was converted back to the percentage of change in RPV per hour by using the following formula: 100 × [1 − exp(β)], where β is the coefficient on the dialysis time. This percentage of change in RPV was then used to determine the significance and strength of association of factors associated with mortality outcomes. The proportionality assumption was tested both by evaluating the log minus log plot and by testing the Schoenfield residuals. Initially, model fits between mortality and RPV volume, UF volume per kilogram, UF rate per kilogram, and RPV slopes were compared without adjustment. We then created multivariate adjusted models. Adjustments were made for the following variables: age, ethnicity, sex, cardiovascular disease, antihypertensive medications, serum albumin, hemoglobin, and dialysis vintage (model 1). Three further models were created that added, in addition to the covariates in model 1, the following covariates: UF volume (model 2); UF volume per postdialysis weight (in kilograms; model 3), and UF rate per postdialysis weight (model 4). Ambulatory systolic BP has been reported previously to be of prognostic value.20 Therefore, an additional model was created by adding interdialytic ambulatory systolic BP to model 4. Adjusted hazard ratios were calculated with continuous covariates (age, albumin, hemoglobin, dialysis vintage, and UF volume) at their group means.

All of the analyses were conducted using Stata 11.0 (Stata Corp). The P values reported are 2 sided and taken to be significant at <0.05.

Results

Between September 2003 and March 2010, 770 patients from 4 dialysis units staffed by the nephrology faculty of Indiana University were screened. Among the screened subjects, 548 qualified, of which 407 consented to participate. Of these, 91 had no RPV monitoring, and 8 had inadequate recordings. The clinical characteristics of the remaining 308 patients dichotomized at a median of RPV slopes are shown in Table 1. The median RPV slope was 1.39% per hour. All of the patients were on thrice-weekly dialysis and were prescribed a dialysis time of ≥4 hours and a blood flow rate of 400 mL/min. The population was predominantly black, with an average age of 54.5 years. Serum albumin and hemoglobin reflect a generally healthier hemodialysis population. Cardiovascular disease defined as previous history of myocardial infarction, coronary bypass surgery or angioplasty, or stroke was present in 34% patients. A majority (79%) of the patients received antihypertensive drugs; β-blockers were used in approximately two thirds, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in approximately half. As expected, those who had flatter slopes and, therefore, possibly more volume overload had lower albumin and lower hemoglobin, reflecting dilutional effects. Those with flatter slopes also gained less interdialytic weight gain and, therefore, had less UF volumes and UF rates. Patients with flatter slopes were older, had more diabetes mellitus, and had higher interdialytic ambulatory systolic BP. A multivariable logistic regression model that included significant predictors from Table 1 demonstrated that only 2 variables were determinants of steeper slopes. These variables were UF rate index (odds ratio: 1.44 [95% CI: 1.30 to 1.59]; P<0.001) and serum albumin (odds ratio: 2.31 [95% CI: 1.04 to 5.13]; P=0.04).

Median follow-up was 30 months (interquartile range: 14 to 54 months), with the longest follow-up of 6.5 years. During this follow-up period, 96 patients (31%) died. The crude mortality rate was 112 per 1000 patient-years. Figure 1 shows the Kaplan–Meier survival curves depicting the relationship between all-cause mortality and median of UF volumes. Survival curves between UF volumes dichotomized at the median were
not found to be of prognostic importance. Similarly, survival based on UF volume per kilogram or UF rate per kilogram of postdialysis weight were not of prognostic value (Table 2). Figure 2 shows the Kaplan–Meier survival curves depicting the relationship between all-cause mortality and median of RPV slopes. Survival curves between RPV slopes dichotomized at the median were found to be prognostically important.

Tables 2 and 3 shows the relationship between volume markers and mortality outcomes by medians RPV slopes. Compared with steeper RPV slope, a flatter RPV slope was

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Table 1. Clinical Characteristics of the Study Population Dichotomized by RPV Slope

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Flat Slope</th>
<th>Steep Slope</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>154 (50)</td>
<td>154 (50)</td>
<td>308 (100)</td>
<td></td>
</tr>
<tr>
<td>RPV slope (%/h)</td>
<td>0.7±0.4</td>
<td>2.6±1.0</td>
<td>1.6±1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, y</td>
<td>56.7±11.9</td>
<td>52.3±13.5</td>
<td>54.5±12.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>98 (64)</td>
<td>108 (70)</td>
<td>206 (67)</td>
<td>0.2</td>
</tr>
<tr>
<td>Racial category, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>White</td>
<td>12 (8)</td>
<td>25 (16)</td>
<td>37 (12)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>139 (90)</td>
<td>126 (82)</td>
<td>265 (86)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>6 (2)</td>
<td></td>
</tr>
<tr>
<td>Years on dialysis</td>
<td>3.5±3.3</td>
<td>3.7±4.4</td>
<td>3.6±3.9</td>
<td>0.6</td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>85 (55)</td>
<td>65 (42)</td>
<td>150 (49)</td>
<td>0.02</td>
</tr>
<tr>
<td>History of cardiovascular disease, n (%)</td>
<td>56 (36)</td>
<td>50 (32)</td>
<td>106 (34)</td>
<td>0.4</td>
</tr>
<tr>
<td>On antihypertensive medications, n (%)</td>
<td>122 (79)</td>
<td>121 (79)</td>
<td>243 (79)</td>
<td>0.9</td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>102 (66)</td>
<td>99 (64)</td>
<td>201 (65)</td>
<td>0.7</td>
</tr>
<tr>
<td>RAAS inhibitors, n (%)</td>
<td>86 (56)</td>
<td>79 (51)</td>
<td>165 (54)</td>
<td>0.4</td>
</tr>
<tr>
<td>Pre-HD weight, kg</td>
<td>83.6±18.5</td>
<td>84.3±21.6</td>
<td>83.9±20.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Post-HD weight, kg</td>
<td>81.0±17.6</td>
<td>80.6±20.9</td>
<td>80.8±19.3</td>
<td>0.9</td>
</tr>
<tr>
<td>UF volume, mL</td>
<td>2116±1135</td>
<td>3396±1291</td>
<td>2756±1372</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>UF/postdialysis weight, mL/kg</td>
<td>26.0±13.3</td>
<td>42.6±14.6</td>
<td>34.3±16.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>UF rate/postweight, mL/kg per h</td>
<td>6.7±3.3</td>
<td>11.3±3.9</td>
<td>9.0±4.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood flow rate, ml/h</td>
<td>397±39</td>
<td>400±34</td>
<td>398±37</td>
<td>0.5</td>
</tr>
<tr>
<td>Dialysate flow rate, ml/h</td>
<td>759±80</td>
<td>766±77</td>
<td>762±79</td>
<td>0.5</td>
</tr>
<tr>
<td>Prescribed dialysis time, min</td>
<td>238±21</td>
<td>238±21</td>
<td>238±21</td>
<td>0.9</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.6±0.4</td>
<td>1.6±0.5</td>
<td>1.6±0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.6±0.5</td>
<td>3.8±0.4</td>
<td>3.7±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.9±1.5</td>
<td>12.4±1.4</td>
<td>12.2±1.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>44-h ambulatory systolic BP, mm Hg</td>
<td>138.7±20.4</td>
<td>133.6±20.8</td>
<td>136.1±20.7</td>
<td>0.04</td>
</tr>
<tr>
<td>44-h ambulatory diastolic BP, mm Hg</td>
<td>78.5±14.3</td>
<td>77.7±14.3</td>
<td>78.1±14.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Data are mean±SD unless otherwise specified. Continuous variables have comparative P values computed by ANOVA. Categorical variables have comparative P values computed by Pearson χ². RAAS indicates renin-angiotensin-aldosterone system; V, volume; K, urea clearance; t, time; HD, hemodialysis.
The results of this study demonstrate the following: (1) RPV slope measurements are of prognostic significance; (2) UF volume alone, UF volume per kilogram, or UF rate indexed for postdialysis weight are of no prognostic significance; and (3) the prognostic relationship of RPV slope to mortality is independent of conventional and unconventional cardiovascular risk factors including UF volume, UF volume per kilogram, and UF rate indexed for postdialysis weight and interdialytic ambulatory BP.

Epidemiological studies have noted that high interdialytic weight gain is associated with higher mortality. Another study noted high interdialytic weight gain to be associated with all-cause and cardiovascular mortality. In unadjusted analyses, we were unable to discover a relationship between interdialytic weight gain and all-cause mortality. This apparently discrepant finding could be attributed to several reasons. First, epidemiological studies that report an unadjusted relationship of interdialytic weight gain and all-cause mortality find only a marginal relationship (P=0.05). This relationship strengthens only after multivariate adjustment. Second, in our study, patients who were recently hospitalized or sick were excluded. Thus, our study differed in its recruitment criteria compared with epidemiological studies, which have analyzed all of the patients in the dialysis unit regardless of their level of illness. In fact, we believe that recent hospitalizations often provoke loss in lean body mass and relative volume excess that may be clinically undetectable. Had we recruited patients who had undergone recent hospitalization, the relationship between RPV slopes and mortality may have been even stronger.

Saran et al have reported among participants in the Dialysis Outcomes and Practice Patterns Study that UF rate indexed for postdialysis weight >10 mL/h per kilogram was associated with a higher risk of mortality (risk ratio: 1.09; P=0.02). In a multivariate model (model 4), we confirmed and extend these observations. We found that RPV slopes were of prognostic value above and beyond UF rate. We interpret this model to mean that patients with higher UF rates have an increased mortality. However, if they have a concomitant flatter slope, they have an even higher mortality.

Among pediatric hemodialysis patients, RPV monitoring has been used to guide dry-weight reduction; this results in lower interdialytic ambulatory BP and reduces the rate of hospitalizations. Similar mechanisms are likely to operate among adults. We speculate that the steeper RPV slopes were associated with lower mortality because patients achieve a more euvoletic state and have less mortality from cardio-

### Table 2. Hazard Ratios for All-Cause Mortality by Median of UF Volume or RPV Slope

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
<th>Model Fit ($\chi^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UF volume</td>
<td>0.78</td>
<td>0.51 to 1.17</td>
<td>0.23</td>
<td>1.45</td>
</tr>
<tr>
<td>UF volume/postdialysis weight</td>
<td>0.79</td>
<td>0.52 to 1.19</td>
<td>0.25</td>
<td>1.3</td>
</tr>
<tr>
<td>UF rate/postdialysis weight</td>
<td>0.89</td>
<td>0.59 to 1.34</td>
<td>0.58</td>
<td>0.6</td>
</tr>
<tr>
<td>RPV slope</td>
<td>1.72</td>
<td>1.14 to 2.58</td>
<td>0.01</td>
<td>6.85</td>
</tr>
</tbody>
</table>

Hazard ratio (HR) is for the upper half compared with lower half. RPV slope compares the hazard ratio of flatter to steeper slope.

Figure 2. Kaplan–Meier survival curves for RPV slope and mortality. The log-rank test demonstrated a significant difference in survival between medians of RPV slopes. Multivariable adjustments did not remove the statistical significance (see Table 2).
vascular causes. In fact, ≥5 groups of investigators have demonstrated the value of RPV monitoring to establish dry weight. These investigations are described here. Lopot et al were among the first to suggest that RPV monitoring may be valuable in the assessment of dry weight. They reported that RPV monitor-guided reduction in dry weight reduced echocardiographic inferior vena cava diameter among patients who were found to be volume overloaded. Rodriguez et al\(^1\) reported in a cohort study of 28 patients that RPV monitoring led to changes in dry weight in all of the patients. Steuer et al\(^2\) reported that 18% of the patients in a dialysis unit had <5% reduction in relative blood volume. Over 6 weeks, they reduced the weight by an average 0.8 kg, which resulted in a larger decrease in relative blood volume with a low incidence of symptoms. Dasselaar et al\(^3\) evaluated the role of blood volume tracking compared with standard therapy in the management of hypertension in hemodialysis patients by reducing dry weight. They reported that, among 14 patients randomized to blood volume tracking-guided dry-weight reduction, predialysis BP was reduced by 22.5/8.3 mm Hg; extracelluar fluid volume and cardiothoracic ratio were also reduced. Sinha et al\(^4\) demonstrated that RPV monitoring can assist in the assessment of dry weight in the context of a randomized, controlled trial. Among participants in the Dry-Weight Reduction in Hypertensive Hemodialysis Patients Trial,\(^5\) RPV monitoring was performed at baseline and at 8 weeks. The intervention group of 100 patients had dry weight probed, whereas 50 patients served as time controls. Probing dry weight in these patients led to steeper slopes; those with flatter slopes at baseline had greater weight loss. Both baseline RPV slopes and the intensity of weight loss were found to be important for subsequent change in RPV slopes. Most important, RPV slopes predicted the subsequent reduction in interdialytic ambulatory systolic BP; those with the flattest slopes had the greatest decline in BP on probing dry weight.

There is one notable exception, a randomized trial that demonstrated that RPV-guided therapy was associated with worse outcomes; this deserves comment. In a multicenter Crit-Line Intradialytic Monitoring Benefit Study,\(^6\) 227 hemodialysis patients were randomized to RPV monitoring and 216 to conventional monitoring for 6 months to test the hypothesis that RPV-guided monitoring would mitigate hospitalization rates. Hospitalization occurred 1.53 times per year in the RPV-guided monitoring group and 1.03 times per year in the conventional group. Mortality was 8.7% and 3.3% (\(P=0.021\)) in the RPV-guided monitoring and conventional monitoring group, respectively. An elaborate protocol was available to guide fluid management based on RPV-guided monitoring. The investigators state, “Algorithm use was encouraged but not mandated, in contrast to earlier studies. This design was intended to assess the therapeutic efficacy of Crit-Line in a trial that permitted voluntary nonuse of the information from the device... Therefore, Crit-Line was studied as a voluntary adjunct to care.”\(^7\) Furthermore, they state, “highly variable implementation of the monitoring and interventional algorithm occurred within and across dialysis units; the causes were not collected.”\(^7\) Uncertain adherence to the protocol by the investigators makes it difficult to conclude that RPV-guided monitoring was a cause of higher complication rates. In fact, at baseline, as determined by RPV slope patterns, patients in the conventional group were more volume overloaded compared with those in the RPV-guided group. At 6 months, both groups had similar RPV slopes. In other words, the conventional group appeared to have had greater volume challenge than the intervention group. Because this study appears to be more observational than interventional due to uncertain adherence to protocol, a more valid evaluation of this technology would have been to compare the RPV slope data as we present in our analysis.
There are several strengths and limitations of our work. As with any cohort study, this study cannot establish a cause-and-effect relationship between volume and mortality. Our study had few white people, and we excluded certain patients, such as those with morbid obesity and atrial fibrillation. Whether the same results would hold in people of broader clinical characteristics is not known and will require verification in future cohorts. Although this is the largest outcome study related to RPV slopes among dialysis patients reported to date, the sample size of our study was still relatively small. RPV was measured at only 1 time point. Repeated measurements would answer the question of whether changes in RPV slopes are prognostically informative. We only studied all-cause mortality; perhaps the value of RPV monitoring would be greater had we studied heart failure hospitalization. Residual renal function was not measured, but given similar vintage of dialysis between groups, it is unlikely that the residual renal function was markedly different between groups. Some strengths of our study are as follows: (1) we used multivariable adjustment to ascertain the independent effect of RPV slope on outcomes; (2) we accounted for the UF volume and UF rates in our model; and (3) we demonstrated that RPV slopes are independent even from interdialytic ambulatory BP. Accordingly, it is unlikely that the results of our study are simply because the RPV slopes were altered by aggressive UF rates.

**Perspectives**

This study extends our earlier diagnostic test study, which demonstrated that RPV slopes reflect volume excess. We now show that flatter RPV slopes that appear to detect hyervolemia among chronic hemodialysis patients are of prognostic value. We believe that next steps are to perform, in a broader group of chronic hemodialysis patients, randomized trials based on RPV slopes to assess heart failure and volume-related hospitalizations. Among chronic dialysis patients, close attention to volume control has the potential to make a difference to the dismal cardiovascular mortality.

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**Disclosures**

None.

**References**

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