Postdialysis Hypertension: Associated Factors, Patient Profiles, and Cardiovascular Mortality

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BACKGROUND AND OBJECTIVES
A postdialytic increase in blood pressure (BP) is a recognized but often an overlooked complication. The epidemiology and predisposing factors are still not well defined. We studied a large sample of Italian dialysis patients to assess the prevalence of postdialysis hypertension (PDHYPER), defined as any increase of systolic BP (SBP) >10 mm Hg above the predialysis value, the associated factors and its role in cardiovascular (CV) mortality.

PATIENTS AND METHODS
In this observational study, we assessed dialysis associated changes in BP in 4,292 hemodialysis (HD) patients over 1 month (51,504 sessions). We compared the clinical characteristics of the patients with stable BP values during the HD session with those with PDHYPER. We also assessed the impact of PDHYPER on CV mortality.

RESULTS
A total of 994 (23.1%) patients had PDHYPER. Patients with PDHYPER were more likely to be hypertensive, older, have a shorter dialysis vintage, be male, have lower SBP, lower changes in weight during HD, and receive more antihypertensive medications. These predictive factors were shown to be associated with an interaction between weight loss and dialysis, suggesting a volume-related mechanism in its pathogenesis. PDHYPER was also associated with CV mortality.

CONCLUSIONS
In our study on a large Italian cohort of dialysis patients, the prevalence of PDHYPER was higher than what was previously reported and is a significant risk factor for CV mortality in dialysis patients. The pathogenesis is multifactorial but hypertensive state, antihypertensive medications, and extracellular volume expansion appear to play a major role.

Keywords: blood pressure; hemodialysis; hypertension; postdialysis hypertension; volume expansion.

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An increase in blood pressure (BP) during hemodialysis (HD), although recognized for many years, is often overlooked.¹ There is also a lack of a unifying criteria for the diagnosis of postdialytic hypertension (PDHYPER), although an increase in systolic BP (SBP) >10 mm Hg from pre- to postdialysis has been proposed and is widely used.² There is also a scarcity of systematic studies on its prevalence and consequences.³ Research on the mechanisms causing PDHYPER has been addressed to both the HD treatment and patient characteristics. The results obtained are often conflicting. Among the possible pathogenetic mechanisms, ultrafiltration-induced hypovolemia may trigger the renin–angiotensin system and induce vasoconstriction, which is mediated by an increase in blood viscosity/hemoconcentration favored by higher hemoglobin (Hb) levels and/or treatment with erythropoiesis stimulating agents.⁴ The removal of antihypertensive drugs by dialysis is another possible cause of intradialytic hypertension. Finally, electrolyte disequilibrium, sympathetic over activity, and endothelial cell dysfunction may play a role.⁵

Unfortunately, the majority of the available studies considered 1 single hypothetical factor at a time or were performed on a small number of patients from a single center. This represents a potential bias since, in general, a single center has a homogeneous policy on the dialytic and medical management of patients. A step forward toward its better understanding can help reduce the high rate of cardiovascular (CV) morbidity occurring in HD patients.⁶

The aim of this large, multicenter, observational study is to investigate HD- and patient-related factors associated with PDHYPER and its impact on mortality.

PATIENTS AND METHODS
Study design
The study is a retrospective analysis of data collected for a previous prospective study.⁷ In brief, patients were assessed at enrollment and were followed thereafter. CV mortality was drawn from death certificate and reported by participating centers. The information requested from participating units on the cause of death were: death due to cerebrovascular disease, ischemic or hemorrhagic, death due to any CV condition, comprising ischemic heart disease, heart failure, and sudden death.
Patients’ characteristics

All adult patients (≥18 years old), in 77 HD centers across Italy, receiving HD thrice weekly for at least 3 months were considered for inclusion. Patients with body weights less than 35 kg, cachexia due to malignancies, severe malnutrition or with known severe heart disease (New York Heart Association (NYHA) class III or IV) were excluded. The diagnosis of heart failure, assigned to consultant cardiologists of the participating centers, was based mainly on clinical grounds or on the finding of left ventricular ejection fraction <50% at transthoracic echocardiography. Along with BP, the following data were recorded: age, sex, smoking and alcohol intake history, serum cholesterol, body mass index, and a history of diabetes serum albumin, Hb, parathyroid hormone. Recorded parameters concerning dialysis treatment were: length of session and dialysis modality, Kt/V as measured with 2-point Daugirdas formula, Δ body weight during HD (as a proxy of ultrafiltration). Due to the frequent modifications in antihypertensive treatment in dialysis patients, we asked the participating centers to maintain the therapy stable during the 12 dialysis period and to provide information about antihypertensive medication (yes/no). The type and dose of erythropoiesis stimulating agent were also collected. HD modality was divided into 2 categories according to the use of convective techniques.

Blood pressure measurement

In every dialysis unit, BP was measured by trained nurses according to National Kidney Foundation Outcomes Quality Initiative (KDOQI) guidelines.9 The nursing staff was specifically instructed accordingly. Predialysis BP was measured after the patient had been sitting for at least 5 minutes before the needles for dialysis access were placed. Postdialysis BP was measured at least 5 minutes after the end of the procedure for 12 consecutive sessions. Likewise, predialysis and postdialysis pulse pressures were calculated from the measured BP; heart rate (HR) was also recorded.

For the analysis, we used the mean of BP changes in 12 consecutive HD sessions. A change (Δ) in SBP was defined as postdialysis minus predialysis SBP. On the basis of published evidence, showing an increase was associated with a number of complications and with mortality, we defined PDHYPER as being an increase in SBP during HD greater than 10 mm Hg above the predialysis BP measurement.2 According to current guidelines, postdialysis hypotension (PDHYPO) is defined as a decrease of SBP greater than 20 mm Hg below the predialysis value.10

For the analysis, we divided the patients into 3 groups according to SBP changes during HD: group 1: Δ SBP between −20 and + 10 mm Hg, group 2: Δ SBP > +10 mm Hg, group 3: Δ SBP > −20 mm Hg. Patients with heart failure were examined separately.

Statistical analysis

Continuous variables are presented as means and SDs unless otherwise specified. Categorical variables are presented as proportions and compared by Pearson’s χ². Means were compared by the analysis of variance with Dunnett’s post hoc test. To detect the predictors of postdialysis changes in SBP, we performed a multiple regression analysis with Δ SBP as the continuous dependent variable. Logistic regression analysis was used to detect factors associated with PDHYPER as a dichotomous dependent variable. The analysis was also carried out using different thresholds for PDHYPER: 5 and 15 mm Hg. An unadjusted model was built only with the variables that were significant to the model. The adjusted model also included nonsignificant variables. Both models were evaluated for goodness of fit by the Hosmer and Lemeshow test and by the area under the receiver-operating characteristic curve. On the basis of the results of the logistic regression analysis, we investigated biological interaction, as defined by Rothman, among predialysis SBP, Δ weight during HD and the use of antihypertensive medications.11 We calculated the relative excess risk because of interaction (RERI) by using the methods outlined by Andersson et al.12 In the absence of a biological interaction, the RERI is 0. Logistic regression was repeated after stratification by tertiles of weight loss due to dialysis.

Survival analysis

The association between Δ SBP and mortality was assessed by the Cox proportional hazard model. Models were built with the following covariates: age, sex, dialysis vintage, presence of diabetes, CHOL, body mass index, albumin, Hb, parathyroid hormone, Kt/V, Δ weight, and predialysis SBP. The proportional hazards assumption of the models was assessed using the Shoemflnd residuals. In the analysis, the etiology of kidney disease was tested for its association with PHYPER and mortality.

All tests were performed by Stata 11 statistical package (Stata, College Station, TX).

RESULTS

At the baseline, we obtained data from 4,292 dialysis patients (>99% Caucasian) for a total of 51,504 dialysis sessions; 2,353 patients were assessed for the presence of heart failure that was detected in 557 subjects (23.6%). The main characteristics of the whole cohort and those of patients grouped according to SBP changes with dialysis are presented in Table 1. A mean postdialysis SBP increase >10 mm Hg (PDHYPER) was detected in 994 (23.1%) patients, among them 73.5% had a diagnosis of hypertension. In patients with a predialysis SBP <140 mm Hg, the prevalence was 28.7%, in those with a predialysis SBP >140 mm Hg the prevalence was 15.4% (P < 0.001, relative risk 0.537).

Multivariable regression analysis with dialytic Δ SBP as a continuous dependent variable produced a significant model (adjusted $R^2 = 0.212$, $F = 74.1$, $Prob > F = 0.0001$) (Table 2).

Postdialysis hypertension

Compared to patients with no changes in BP (group 1), those with PDHYPER (group 2) were more likely to
be older, have a shorter dialysis vintage, lower body mass index, lower Δ weight during HD, lower Hb, lower parathyroid hormone, lower predialysis SBP, and heart rate. Furthermore, the proportion of patients on antihypertensive medications was higher, as well as the percentage of patients with an ejection fraction <50%. Logistic regression analysis, using PDHYPER as a dichotomous dependent variable, produced 2 significant models (1 adjusted and 1 unadjusted) (Table 3). For the unadjusted model, the area under the receiver-operating characteristic curve was 0.729, correctly classified as 85.34%. The Hosmer and Lemeshow $\chi^2$ was 4.91 with probabilities $> \chi^2 = 0.767.$
For the adjusted model, the area under receiver-operating characteristic curve was 0.732, correctly classified 85.53%. The Hosmer and Lemeshow \[\chi^2\] was 5.50, with probabilities \(\chi^2 = 0.702\). The tests indicated a good discrimination for both models. The use of antihypertensive medications, male sex, increased predialysis pulse pressures, increased age, and longer length of the HD session were significant predictors of PDHYPER. Conversely, Δ weight during HD, erythropoiesis stimulating agent use, predialysis SBP, and predialysis HR were predictors, inversely associated, of postdialysis hypertension. Diabetes and heart failure were found not to be predictors. The analysis, repeated after stratification by tertiles of weight loss by dialysis, showed that the following variables were significantly predictive: use of antihypertensive medications, predialysis SBP, and predialysis pulse pressures. Logistic regression was also carried out with 2 different thresholds for PDHYPER (5 and 15 mm Hg). With the 5 mm Hg threshold, found in 28.7% of the patients, the results were concordant with those obtained with the 10 mm Hg threshold. Raising the threshold to 15 mm Hg, 10.5% of the patients presented PDHYPER. In the analysis, only age, Δ weight, and heart rate were significant predictors.

**Interaction between factors**

We found a significant interaction between predialysis SBP and Δ weight during HD (RERI −2.830, confidence interval (CI) −3.088 to 2.573), between Δ weight during HD and the use of antihypertensive medications (RERI −1.881, CI −2.631 to 1.131) and between predialysis SBP and use of antihypertensive medications (RERI −1.793, CI −2.572 to 1.015). These values indicate interaction on an additive scale, meaning that the combined effect is less than the sum of the factors examined singly.

**Patients with heart failure**

The logistic regression performed in patients with heart failure showed the following predictors of PDHYPER: predialysis SBP (OR 1.25, CI 1.17–1.34; \(P < 0.001\)), female sex (0.17, CI = 0.05–0.63; \(P = 0.008\)).

**Survival and changes in BP with dialysis**

Patients were followed up for a mean of 26.8 ± 11.1 months; 348 patients who were lost to follow-up were either transplanted or transferred to different units. On the basis of the results of the above logistic regression, we excluded from the analysis subjects with heart failure. We had data for CV mortality in the remaining 3,196 patients, among whom 420 deaths were recorded. Of those, 318 were ascribed to a heart disease and 102 to a cerebrovascular event. The Cox analysis produced a significant model with the following predictors of CV mortality: age (HR 1.05, CI 1.03–1.07; \(P < 0.001\)), dialysis vintage (HR 1.01, CI 1.00–1.02; \(P = 0.038\)), PDHYPER (HR 1.69, CI 1.12–2.57; \(P = 0.012\)) (Figure 1). Predialysis SBP (> or <140 mm Hg) was not a predictor of mortality. Apart from hypertension, no other association was found between the etiology of kidney disease and PHYPER or mortality.

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### Table 3. Unadjusted and adjusted odds ratios for postdialysis hypertension

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unadjusted</th>
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<th></th>
<th>Adjusted</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>(P)</td>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>(P)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.01–1.03</td>
<td>&lt;0.001</td>
<td></td>
<td>1.02</td>
<td>1.01–1.03</td>
<td>0.030</td>
<td></td>
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<tr>
<td>Male sex</td>
<td>1.36</td>
<td>1.04–1.78</td>
<td>0.024</td>
<td></td>
<td>1.33</td>
<td>0.99–1.78</td>
<td>0.058</td>
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<tr>
<td>Dialysis session time</td>
<td>1.01</td>
<td>1.00–1.02</td>
<td>&lt;0.001</td>
<td></td>
<td>1.01</td>
<td>0.99–1.02</td>
<td>0.065</td>
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<td>Δ Weight with dialysis</td>
<td>0.57</td>
<td>0.49–0.68</td>
<td>&lt;0.001</td>
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<td>0.59</td>
<td>0.49–0.70</td>
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<td>Predialysis SBP</td>
<td>0.96</td>
<td>0.95–0.97</td>
<td>&lt;0.001</td>
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<td>0.96</td>
<td>0.95–0.97</td>
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<td>Predialysis PP</td>
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<td>1.01–1.03</td>
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<td>1.02</td>
<td>1.01–1.03</td>
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<td>Predialysis HR</td>
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<td>0.96–0.99</td>
<td>0.030</td>
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<td>0.98</td>
<td>0.96–0.99</td>
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<td>ESA</td>
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<td>0.37–0.79</td>
<td>0.019</td>
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<td>0.55</td>
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<td>Antihypertensive medications</td>
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<td>0.94–1.01</td>
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<td>0.63–1.28</td>
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<td>1.09</td>
<td>0.65–1.81</td>
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<td>Hemoglobin</td>
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<td>0.94</td>
<td>0.87–1.02</td>
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<td>Albumin</td>
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<td>0.99–1.01</td>
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<td>0.99–1.00</td>
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<td>Convective HD</td>
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<td></td>
<td>1.97</td>
<td>0.70–1.34</td>
<td>0.858</td>
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</table>

Abbreviations: CI, confidence interval; ESA, erythropoiesis stimulating agent; SBP, systolic blood pressure; PP, pulse pressure; HR, heart rate; HD, hemodialysis; PTH, parathyroid hormone.
DISCUSSION

PDHYPER is generally perceived as an uncommon complication of dialytic treatment. In different surveys, adopting the same criteria as the present study, the occurrence of an increase in BP from pre- to postdialysis was found in less than 15% of maintenance HD patients. In our large sample of Italian dialysis patients, we showed that PDHYPER is a relatively common phenomenon, occurring in nearly 1 of 4 patients. We also found that the main factors influencing SBP changes during HD were a hypertensive state, predialysis SBP and pulse pressures, pre- and postdialysis HR, Δ weight during HD, Hb, dialytic vintage, and body mass index.

We have also found that, in patients without heart failure, PDHYPER is a significant predictor of CV mortality. The mechanism leading to PDHYPER is not so straightforward. The interaction between the use of antihypertensive medications and Δ weight during HD may suggest an increased need for medications in patients with inadequate intradialytic weight loss compared to their dry weight. Medications explain lower predialysis SBP and their removal with dialysis is a reasonable cause of PDHYPER. Furthermore, these patients are more likely to have a shorter dialysis vintage and thus residual diuresis and/or adherence to a low sodium diet. This setting may lead to a reduced sodium pool, as testified by lower predialysis SBP. A lower Δ weight during HD may lead to reduced convective loss of sodium when using a standard dialysate with a sodium concentration of 139 mEq/l. This may allow a diffusive flux of sodium toward the body compartment, especially in patients with a low predialysis plasma sodium concentration (as is often the case in patients with low sodium intake). The consequence of a positive sodium balance at the end of the dialytic session is an increase in extracellular fluid volume that may be overlooked. The end of the process is a positive sodium balance with consequent hypertension requiring ever more antihypertensive medications. A longer duration of the dialysis session, which is associated with postdialysis hypertension, may increase drug removal and give more time for the diffusive transport of sodium from the dialysate to the plasma and, thus, a more positive sodium balance. Unfortunately, we did not collect information regarding sodium concentrations in plasma and in dialysate to better support this hypothesis. Nevertheless, this interpretation is in line with data from small cohorts of dialysis patients and experimental studies aimed at investigate specific mechanisms of PDHYPER. In a post hoc analysis of the Dry-weight reduction in hypertensive hemodialysis patients (DRIP) trial, the authors measured the slopes of intradialytic BP during dialysis and tested the effect of dry-weight reduction on these slopes and found that intradialytic BP changes were associated with changes in dry body weight. These results suggested that PDHYPER is a marker of volume excess. Recently, Nongnuch et al submitted 531 dialysis patients to multiple-frequency bioelectrical impedance and found that the ratio of extracellular water to total body water was significantly higher in the patients with PDHYPER.
The prevalence of heart failure in dialysis patients is high and the prognosis is ominous, especially in the presence of hypertension. In patients with heart failure in our study, the factors associated with PDHYPER were not the same as the ones we found in the others. Interestingly, Δ weight was not a predictor, indicating a more complex mechanism operating in this subset of patients. Predialysis SBP was a more significant predictor. These findings show that factors associated with changes in BP during dialysis vary according to the individual characteristics of patients.

Our study has a number of limitations. We did not perform a direct examination of extracellular volume. Thus, we can give only indirect evidence about the causative effect of volume expansion on PDHYPER and we cannot rule out other contributing factors, such as diastolic sodium concentration, renin–angiotensin–aldosterone system, and sympathetic activation. We did not collect information on the class and number of antihypertensive medications. Thus, we can just speculate around medication removal by dialysis. On the other hand, the large number of enrolled patients and collected variables, together with the homogeneity of the population, strengthen the validity of the results obtained. In conclusion, our multicenter study shows that the prevalence of PDHYPER is higher than that previously reported and that it is associated with high CV mortality.

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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES