Pulmonary hypertension is prevalent in catheter and arterio-venous access hemodialysis

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Abstract

Pulmonary hypertension (PH) has been described in patients undergoing hemodialysis and proposed to arise from overflow in arterio-venous grafts or fistulae. Whether PH is prevalent in patients undergoing catheter-based dialysis is unknown. Patients undergoing hemodialysis with an echocardiogram in two urban dialysis centers over a four-year period were included. Demographic data, comorbidities, dialysis access, laboratory and echocardiographic data were collected. A right ventricular systolic pressure of ≥45 mmHg defined PH. Forty out of ninety-one (44%) patients met the criteria for PH. The prevalence of catheter-based hemodialysis was similar in the two groups (30% in the PH vs. 33% in the no-PH group). PH patients were more likely to have extended hemodialysis vintage (52.6±58.2 vs. 31.0±33.7 months, P<0.05). Advanced left heart disease was not more prevalent in patients with PH although they were more likely to have right atrial and right ventricular enlargement (P<0.05). Mean serum phosphate was lower in the PH group (4.7±1.4 vs. 5.5±1.8 mg/dL, P<0.05). On multivariate analysis, lower phosphate levels were associated with higher risk of PH. We concluded that PH is prevalent in hemodialysis regardless of access type and may be because of disordered calcium and phosphate metabolism.

Introduction

Cardiovascular disease is a well-recognized and important source of mortality in patients with chronic kidney disease.1,2 Thus, despite advances in the care of patients undergoing renal replacement treatment, mortality remains unacceptably elevated, highlighting the potential for advancing cardiovascular care of patients with chronic kidney disease.3 Aside from coronary artery disease, other forms of cardiovascular disease are also prevalent in chronic kidney disease. Pulmonary hypertension (PH) has been described in patients undergoing renal replacement with hemodialysis through an arterio-venous graft or fistula,4,5 where pulmonary vascular disease may be multifactorial.4,5 Chronic volume overload can predispose to pulmonary venous hypertension. Alternatively, metabolic derangements associated with chronic kidney disease may affect the pulmonary vasculature directly or indirectly. Alterations in calcium and phosphate absorption and excretion may result in metastatic pulmonary artery calcification.6 Others have shown that chronically increased blood flow from arterio-venous fistulae or grafts results in overflow-induced PH.7 Furthermore, procedures such as access thrombectomy may predispose to small pulmonary emboli causing elevated pulmonary pressures.8 Lastly, underlying diseases such as scleroderma or systemic lupus erythematosus may alter susceptibility to the factors described above or directly affect the pulmonary vasculature.

Previous studies of PH and end-stage renal disease (ESRD) have been unable to determine the relative contribution of metabolic derangement and increased flow as they have included patients with surgical arterio-venous fistulae exclusively.4,5 Our dialysis population included a substantial population of patients undergoing catheter-based hemodialysis and we had observed that a number of them had pulmonary vascular disease. The prevalence of PH in patients with catheter-based dialysis is unknown thus far. We hypothesize that PH is prevalent in patients with ESRD undergoing hemodialysis regardless of access route and, therefore, that PH is not solely a result of chronic overflow associated with arterio-venous shunt.

Materials and Methods

Patient selection

All patients aged 18 years or older undergoing hemodialysis from August 2001 to June 2005 at two centers associated with our institution, and who also had echocardiography for clinical indications (including evaluation of left or right heart function, concern for valvular heart disease, preoperative evaluation), were identified. Charts were analyzed for demographic characteristics, data obtained from echocardiography, laboratory results obtained within three months of the time of the echocardiogram, and route of dialysis from the dialysis record. There were no exclusion criteria. An Institutional Review Board approval was obtained from Johns Hopkins Hospital for this study.
Hemodialysis protocol

Hemodialysis procedure was conducted thrice weekly and all patients received erythropoietin treatment to maintain hematocrit values in the range of 33-36%.

Clinical data

Demographic information including age, gender, and ethnicity was recorded. In addition, underlyng cause of ESRD, length of time on dialysis, and medical comorbidities were extracted. Laboratory data including BUN, creatinine, serum calcium, phosphate, albumin, hematocrit, and intact parathyroid hormone (PTH) were recorded.

Transthoracic echocardiography

Two-dimensional and M-mode transthoracic echocardiography was performed on all subjects at a single institution. Echocardiography was done for clinical indications and thus was not standardized for time from dialysis. Chamber size, the presence of valvular regurgitation, and estimated right ventricular systolic pressure were recorded in all patients when possible. PH was defined by a right ventricular systolic pressure (RVSP) estimated as >45 mmHg. In the nine patients in whom tricuspid regurgitation was present but unable to be quantified, the RVSP was assumed to be 20 mmHg if there was no evidence of right ventricular dilation and right ventricular systolic function was not to be abnormal. If there was no tricuspid regurgitation, RVSP was assumed to be 20 mmHg.11-13

Statistical analysis

Unless specified, data are presented as mean±SD. The χ²-test was used to compare differences between populations. The Student t-test was used for analysis of continuous data. Multivariate logistic regression models were used to identify independent predictors of PH, adjusting for age, gender, and ethnicity. The statistical packages Graphpad Prism 5.0a and Stata 9.0 (College Station, TX) were used for the analysis. A P<0.05 was considered statistically significant.

Results

A total of 91 patients meeting study criteria were identified. The study population had a mean age of 52.8±14.7 years, and was predominantly female and African American, 58% and 89%, respectively. The mean dialysis vintage was 40.5±47.0 months, with a median of 24 months and a range of 0-324 months. Underlying diabetes, hypertension, or both were the most common causes of ESRD (49/91, 54%). A significant portion of the total

| Table 1. Characteristics of patients by dialysis access. |
|----------------------------------------------------------|
| **Catheter** (n=29) | **AV graft or fistula** (n=62) | **P**  |
| **Age (years)** | 54±15 | 51±14 | 0.5  |
| **Gender (female/male)** | 9/20 | 33/29 | 0.05* |
| **HD vintage (months)** | 46.3±68.3 | 37.8±33.7 | 0.4  |
| **HIV positive (%)** | 16 | 21 | 0.6* |
| **RVSP (mmHg)** | 41.3±17.7 | 44.3±15.9 | 0.4  |
| **Calcium (mg/dL)** | 11.2±11.2 | 9.1±0.9 | 0.2  |
| **Phosphate (mg/dL)** | 4.6±5.6 | 4.7±5.7 | 0.9  |
| **iPTH (pg/mL)** | 318.2±332.3 | 468.3±662.4 | 0.3  |
| **Hct (%)** | 33.8±6.1 | 33.9±5.3 | 0.8  |

Data are presented as mean±SD unless otherwise noted. T-test used unless otherwise noted (*χ² test). HD, hemodialysis; RVSP, right ventricular systolic pressure; iPTH, intact parathyroid hormone; Hct, hematocrit.

| Table 2. Clinical and laboratory data in patients with and without pulmonary hypertension. |
|----------------------------------------------------------|
| **No-PH** (n=51) | **PH** (n=40) | **All** (n=91) | **(no-PH vs. PH)** |
| **Age (years, mean±SD)** | 50.9±14.7 | 55.2±14.7 | 52.8±14.7 | 0.2* |
| **Gender (female/male)** | 32/19 | 21/19 | 53/38 | 0.3  |
| **Race (n)** | 45 | 36 | 81 | 0.5  |
| **Comorbidities (n)** | 16 | 10 | 26 | 0.5  |
| **Cause ESRD (n)** | 14 | 16 | 30 | 0.7  |
| **Diabetes** | 8 | 9 | 14 | 0.8  |
| **Hypertension** | 9 | 7 | 16 | 0.8  |
| **HIV** | 8 | 1 | 9 | 0.004 |
| **FSGS** | 4 | 5 | 9 | 0.9  |
| **Miscellaneous** | 5 | 2 | 7 | 0.1  |
| **HD Vintage (month)** | 31.9±33.7 | 52.6±58.2 | 40.6±47.0 | 0.02* |
| **HIV positive (n)** | 7 | 9 | 16 | 0.8  |
| **Medication use (%)** | 61 | 65 | 62 | 0.7  |
| **ACEI or ARB** | 67 | 70 | 68 | 0.2  |
| **Dialysis access** | 34 | 28 | 60 | 0.6  |
| **AV graft/fistula** | 17 | 12 | 25 | 0.9  |

χ² test done unless otherwise noted (*t-test used, **data available on 74 patients). PH, pulmonary hypertension; ESRD, end-stage renal disease; HD, hemodialysis; B blocker, β-blocker; FSGS, focal segmental glomerulosclerosis; ACE, angiotensin II converting enzyme; ARB, angiotensin receptor blocker; RVSP, right ventricular systolic pressure; iPTH, intact parathyroid hormone; Hct, hematocrit.

| Table 3. Laboratory data (mean±SD). |
|-------------------------------------|
| **No PH** | **PH** | **All** | **P** |
| **Calcium (mg/dL)** (n=89) | 8.9±1.0 | 9.1±0.7 | 9.0±0.9 | 0.5  |
| **Albumin (g/dL)** (n=89) | 3.4±0.6 | 3.3±0.6 | 3.4±0.6 | 0.8  |
| **Corrected Ca (mg/dL)** (n=89) | 9.5±0.9 | 9.6±0.7 | 9.5±0.8 | 0.2  |
| **Phosphate (mg/dL)** (n=88) | 5.5±1.8 | 4.7±1.4 | 5.1±1.6 | 0.04 |
| **Calcium X phosphorous (mg/dL)** (n=88) | 51.5±17.0 | 45.6±13.4 | 48.9±15.7 | 0.08 |
| **iPTH (pg/mL)** (n=71) | 359.3±376.0 | 476.0±323.5 | 413.6±568.7 | 0.4  |
| **BUN (mg/dL)** (n=89) | 47.3±17.8 | 43.5±20.6 | 45.6±19.0 | 0.4  |
| **Creatinine (mg/dL)** (n=89) | 8.6±2.9 | 7.2±3.6 | 8.0±3.2 | 0.04 |
| **Hct (%)** (n=89) | 34.4±6.0 | 33.0±4.8 | 33.8±5.5 | 0.2  |

T-test used; iPTH, intact parathyroid hormone; Hct, hematocrit.

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population, 29/91 (32%), was receiving hemodialysis through a catheter. Of the remainder, 41/91 (45%) patients were using a fistula and 21/91 (23%) had an AV graft. Mean dialysis vintage in the group with an AV graft or fistula was not different from the catheter-based dialysis group (P=0.24, Table 1). There were no significant differences between the AV graft or fistula group and the catheter-based dialysis group with the exception of patients with a catheter who were more likely to be male (P=0.05). Overall, 40/91 (44%) patients had an RVSP of ≥45 mmHg, defining PH. Clinical and laboratory data of the 91 patients segregated by the presence or absence of PH are shown in Table 2. There were no differences in age, gender, or ethnicity in those with or without PH. Both groups were predominantly female and African American. All patients with focal segmental glomerulosclerosis (FSGS) were HIV negative. Patients with PH were more likely to have undergone extended hemodialysis with a mean vintage of 52.6±58.2 months vs. 31.0±33.7 months in those without PH (P=0.02). However, HIV status and presence of diabetes or systemic hypertension were not associated with the presence of PH. Use of β-blockers and ACE inhibitors (ACEI) or angiotensin receptor blockers (ARB) was prevalent and similar in the two groups. In those patients without PH, 17/51 patients (33%) were undergoing dialysis through a catheter compared to 12/40 patients (30%) with PH (P=0.9).

Echocardiographic data of patients with and without PH are shown in Figure 1. Measures of left ventricular function including the presence of left ventricular or atrial enlargement and left ventricular ejection fraction were similar in both groups. Mean left ventricular ejection fraction was 55.5±13.4% in the group without PH and 50.5±16.7% in the group with PH. Tricuspid regurgitation was more likely to be present in the group with PH (100% vs. 84%, P=0.006), but was equally prevalent in patients with and without catheter-based hemodialysis (95% vs. 89%, P=0.51). Consistent with the presence of significant PH and associated right heart dysfunction, right ventricular and atrial dilation were more likely to be present in the PH group (33% vs. 16%, P<0.0001, and 53% vs. 16%, P=0.0003). Mean RVSP in patients with a catheter was 39.6±16.17 and 45.84±16.30 mmHg in those with AV graft or fistula, P=0.1 (Figure 2).

The mean phosphate level was lower in those patients with PH than those without (Table 3). Concomitantly, there was a trend toward lower serum calcium and phosphate products (corrected calcium multiplied by phosphate) and higher intact PTH levels in the group with PH, although this did not meet statistical significance. Creatinine was significantly lower in the group with PH. In multivariate analyses adjusting for age, gender, and ethnicity, the presence of lower phosphate was associated with PH.

Discussion

We studied the prevalence of PH in a cohort of patients undergoing hemodialysis through an AV graft, fistula, or catheter and found a prevalence of 44% in the group as a whole without a significant difference in prevalence of PH based on hemodialysis access. Surprisingly, we additionally showed that lower phosphate is associated with PH. Previous studies have shown a high prevalence of PH in patients undergoing hemodialysis via AV graft or fistula.5,6,14-16 These studies have demonstrated potential mechanisms of PH by compression of the AV access and showing improvement in PA pressure,5,6 implicating several potential vasoactive mediators, such as endothelin, nitric oxide metabolites, thromboxane, and markers of calcium homeostasis in the pathogenesis of PH.5,6,14-16 Others have shown a high prevalence of left ventricular hypertrophy in the patients with PH and ESRD.17,18 Pulmonary artery calcification has not been shown to be associated with PH to those without, making anemia an unlikely cause of overflow-associated PH. All patients were treated with erythropoietin, thus this potential growth factor was present in all patients.

There has been prior investigation into the role of disordered mineral metabolism in patients with ESRD and PH. This is an attractive hypothesis since excessive vascular calcification is not infrequent in patients with ESRD. Vascular calcification is associated with increased vascular stiffness, leading to PH.19 Pulmonary artery calcification has not been shown to be associated with PH in this population,19 and our data corroborates this finding. However, PTH levels were elevated in one cohort of patients with PH and ESRD.1 In our study, phosphate levels were lower in the
group with PH, and there was no significant difference in PTH levels in the two groups although there was a trend to higher levels in the group with PH. These findings should be interpreted with caution given the cross-sectional nature of our study. The wide variation in PTH levels in the cohort and the relatively small sample size may account for the difference between our data and that previously published. Furthermore, our study was not designed to determine the association of disordered mineral metabolism and PH. Phosphate content in the pulmonary media, mediators of calcifications, or levels of calcification inhibitors may be of more relevance than merely serum phosphate level. Alternatively, our finding of lower phosphate in the PH group may suggest a different signaling pathway underlying PH in ESRD, perhaps related to endothelial dysfunction, not simply vascular stiffness. Although phosphate and PTH are not known to be pulmonary vasoactive substances, their alterations may be markers of metabolic derangement predisposing to PH.

Our study population was an urban, predominantly African American group, which compares to prior publications of PH in ESRD that have been reported primarily from the Middle East.\cite{5,12,14} Although the numbers were small, there were significantly more patients with FSGS in the group with PH. Previous studies did not have substantial numbers of patients with FSGS. Our sample included a significant portion of patients with HIV, though this did not associate with PH. The absence of a correlation here may be because of sample size, as pulmonary arterial hypertension occurs in only a small fraction of patients with HIV.\cite{19,21,23} Like other cohorts, our patients with PH were predominantly female, as has been described in patients with pulmonary arterial hypertension,\cite{28} perhaps reflecting pulmonary vascular predisposition to hypertension in women.\cite{29}

The data collected in this study do not allow further classification of PH according to the WHO schema.\cite{30} Indeed, a portion of our patients likely had pulmonary venous hypertension associated with systemic hypertension and left ventricular diastolic dysfunction. Emboli, as a result of either surgical graft manipulation\cite{10} or clot dislodgement from catheters or grafts, may also play an important role in PH in patients with ESRD. Nonetheless, the right ventricular changes seen on echocardiography suggest that PH is likely to be of hemodynamic significance in this population, and therefore, whether because of pulmonary venous hypertension or pulmonary arterial hypertension, may have an important effect on mortality.\cite{14,21} Moreover, these data suggest that PH in ESRD is, at least in part, a result of factors other than a high output state associated with the arteriovenous shunt and may, in fact, be because of endothelial dysfunction. If volume optimization does not reverse findings suggestive of PH on echocardiography, further evaluation to characterize the disease should include right heart catheterization to confirm PH and rule out a pulmonary venous component, and performing additional studies such as a ventilation-perfusion lung scan to exclude chronic thromboemboli.

Our data are limited by retrospective collection and a heterogeneous population of patients that had echocardiography done for clinical indications, which may enrich the population with significant cardiopulmonary disease and provide a source of bias in the data. Additionally, we did not directly measure cardiac output or perform right heart catheterization on this retrospective population of patients. Nonetheless, ours is the first data to show that PH is prevalent in ESRD regardless of dialysis access type and may not be solely because of overflow. Furthermore, we are the first to report on the association of PH with ESRD in a Western population.

We conclude that PH is prevalent in ESRD regardless of dialysis access. Disordered calcium and phosphorous metabolism may potentially be involved, although prospective studies are much needed to explore this association further. Additionally, the clinical significance, exact classification, and etiology of PH in ESRD require further investigation.

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