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Pulmonary Hypertension in Peritoneal Dialysis Patients

The information available in the literature regarding pulmonary hypertension (PH) in peritoneal dialysis (PD) patients is limited. The objective of the present study was to examine the prevalence and characteristics of PH in PD patients.

We retrospectively collected the clinical profile, echocardiographic (ECHO) findings, and biochemical data for 36 PD patients for which ECHO findings were available. We compared characteristics between patients with and without PH. We found PH, defined as pulmonary arterial pressure (PAP) ≥ 35 mmHg, in 15 patients. The prevalence of PH was 42%. Mean age (\pm standard deviation) of the patients with and without PH was 58 ± 15 years and 52 ± 15 years respectively ($p = 0.30$). Mean PAP of the PH patients was 43.8 ± 9.0 mmHg (range: 35 – 65 mmHg).

Patients with PH had a lower ejection fraction than did patients without PH ($46.3\% \pm 19.8\%$ vs. $56.5\% \pm 11.8\%$ respectively, $p = 0.07$). Patients with PH also had a higher prevalence of global hypokinesia (60% vs. 29%, $p = 0.059$) and dilated left ventricular chamber (53% vs. 19%, $p = 0.03$). In PH patients, body mass index (24 ± 4.5 kg/m² vs. 28 ± 5.0 kg/m², $p = 0.024$), normalized protein catabolic rate (0.78 ± 0.21 g/kg vs. 0.95 ± 0.27 g/kg daily, $p = 0.049$), and ferritin (226 ± 210 ng/mL vs. 873 ± 965 ng/mL, $p = 0.005$) were significantly lower and lactate dehydrogenase was higher (264 ± 99 U/L vs. 206 ± 79 U/L, $p = 0.06$) than in patients without PH. We observed no significant differences in race or sex, incidence of hypertension or cardiovascular disease, or vitamin D analog use between the two groups of patients. During the study period, 60% of PH patients and 38% of patients without PH died ($p = 0.19$). Values of PAP correlated directly with serum levels of phosphorus ($r = 0.44$, $p = 0.02$), Ca \times P product ($r = 0.40$, $p = 0.04$), and parathyroid hormone ($r = 0.42$, $p = 0.03$). Of continuous ambulatory PD and continuous cycling PD patients, 21% and 55% respectively had PH ($p = 0.049$). In PD patients, PH

is highly prevalent and may be associated with higher mortality risk.

Key words

Pulmonary hypertension, parathyroid hormone, PTH, pulmonary arterial pressure, mortality

Introduction

Pulmonary hypertension (PH) is increasingly being recognized as a factor that can affect outcome in end-stage renal disease (ESRD). Most cases of PH are consequent to myocardial or pulmonary diseases. Chronic left ventricular failure and the resulting elevation in pulmonary venous pressure is the most common cause of PH. In several populations without chronic kidney disease (CKD), PH has been associated with excess mortality (1–3). A high prevalence of PH in CKD patients on hemodialysis (HD) has recently been reported (4–7). In a retrospective study (8), we reported PH in 64% of HD patients who underwent echocardiography (ECHO) for any reason within the preceding 12 months (36% of our entire HD population, reflecting the minimum prevalence).

End-stage renal disease commonly occurs with significant comorbidities, several of which may lead to PH. Left-side heart disease, chronic obstructive pulmonary disease, sleep apnea, collagen vascular diseases, HIV infection, and portal hypertension may coexist and result in PH. Most HD patients have an arteriovenous (AV) hemoaccess that results in AV shunting and potentially in PH. In addition, secondary hyperparathyroidism, elevated Ca \times P product, and vascular calcification are commonly seen in CKD patients (9,10).

In an animal model, Akmal *et al.* showed that excess parathyroid hormone (PTH) in chronic renal failure induces pulmonary calcification, PH, and right ventricular hypertrophy (11). Recently, we reported the prevalence and clinical characteristics of PH in CKD patients before initiation of renal replacement therapy (12).

The information available in the literature regarding PH in patients treated with peritoneal dialysis (PD)

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is limited (4). The objective of the present study was therefore to examine the prevalence, clinical profile, and echocardiography characteristics of PH in PD patients and to identify the biochemical markers associated with PH in PD patients.

Patients and methods

We retrospectively reviewed the medical records of 80 PD patients treated at the Avram Center for Kidney Diseases (the outpatient facility at Long Island College Hospital) between 2002 and 2005. Of these patients, 36 had undergone ECHO.

On patient enrollment into the study, we collected demographic data (including age, race, and sex) and clinical data (including body weight, body mass index, presence of diabetes and hypertension, known cardiovascular or pulmonary disease, medication history, and tobacco and alcohol use). Biochemical parameters and ECHO findings were collected for each patient. Laboratory data nearest to the patient's ECHO study were included in the analysis. We defined PH as a systolic pulmonary artery pressure (PAP) \geq 35 mmHg (4). For 8 patients whose PAP was not recorded, we presumed a lack of PH.

We compared characteristics between patients with and without PH. The Institutional Review Board of Long Island College Hospital approved the study protocol.

Statistical analyses

Continuous variables are reported as mean \pm standard deviation. For selected comparisons between two group means, the parametric (*t*-test) or nonparametric (Mann-Whitney test) was used, as applicable. Categorical variables were compared using the chi-square test or the Fisher exact test, as appropriate. Correlations were reported either as Pearson correlation coefficients or Spearman rank correlation coefficients. Calculations were performed using SPSS 12.0.1 for Windows (SPSS Inc., Chicago, IL, U.S.A.).

Results

Of the 36 PD patients, 15 had PH, a prevalence of 42%. For the groups without and with PH, we observed no differences in age (52 ± 15 years vs. 58 ± 15 years, $p = 0.30$), sex (women: 62% vs. 53%), race (African American: 71% vs. 73%), or cause of CKD.

Table I compares the clinical characteristics of patients without and with PH. Surprisingly, the patients

without PH had a higher prevalence of diabetes (57% vs. 20%, $p = 0.04$) and peripheral vascular disease (29% vs. 0%, $p = 0.03$). Patients with PH had higher prevalences of congestive heart failure (CHF: 13% vs. 0%; $p = 0.08$) and coronary artery disease (CAD: 40% vs. 14%; $p = 0.08$). The percentage of smokers was higher among PH patients than among those without PH (53% vs. 24%, $p = 0.07$). During the study period, 60% of the PH patients and 38% of the patients without PH died ($p = 0.31$), highlighting the risk accompanying PH in this population.

Table II shows biochemical parameters for patients without and with PH. Patients with PH had a significantly lower normalized protein catabolic rate (0.78 g/kg vs. 0.95 g/kg, $p = 0.049$), significantly lower ferritin (227 ng/mL vs. 873 ng/mL, $p = 0.008$), and higher lactic dehydrogenase (LDH: 264 U/L vs. 206 U/L; $p = 0.06$).

Values of PAP were not normally distributed in PD patients. Mean and median PAP were 37.4 ± 9.96 mmHg and 35 mmHg overall, with a range of 25 – 65 mmHg. Among PH patients, mean PAP was 43.8 ± 9.0 mmHg (range: 35 – 65 mmHg). Values of PAP correlated positively with serum levels of phosphorus ($r = 0.44$, $p = 0.02$), $\text{Ca} \times \text{P}$ product ($r = 0.40$, $p = 0.04$), and parathyroid hormone (PTH: $r = 0.42$, $p = 0.03$; Figure 1), and negatively with serum ferritin ($r = -0.46$, $p = 0.016$).

Table III shows the ECHO characteristics of the patients without and with PH. Although the *p* value did not quite reach significance, patients with PH had a lower left ventricular ejection fraction than did patients without PH (46.3% vs. 56.5%, $p = 0.07$). As compared with patients without PH, patients with PH had significantly greater prevalence of dilated left chamber (53% vs. 19%, $p = 0.03$) and global hypokinesia (60% vs. 29%, $p = 0.059$).

We also compared the history of medications and dialysis modality use between the two groups of PD patients. As expected, because of a higher prevalence of diabetes, patients without PH were more likely to be taking insulin ($p = 0.01$). We observed no significant difference between the two groups of PD patients with regard to treatment with erythropoietin, vitamin D analogs, phosphate binders, angiotensin converting-enzyme inhibitors, beta-blockers, and calcium channel blockers. Of continuous ambulatory PD patients and continuous cycling PD patients, 21% and 55% respectively had PH ($p = 0.049$).

TABLE I Clinical characteristics of peritoneal dialysis patients without and with pulmonary hypertension (PH)

	Without PH (n=21)	With PH (n=15)	p Value
Body mass index (kg/m ²)	28±5.0	24±4.5	0.024
Hypertension (%)	90.5	93.3	0.63
Diabetes (%)	57	20	0.04
Coronary artery disease (%)	14	40	0.08
Congestive heart failure (%)	0	13	0.08
HIV-positive (%)	9.5	13	0.72
Peripheral vascular disease (%)	29	0	0.03
Smoking (%)	24	53	0.07
Residual GFR (mL/min)	0.58±0.86	0.70±1.3	0.58
Residual renal function (%)	43	27	0.32
Expiration (%)	38	60	0.19

GFR = glomerular filtration rate.

TABLE II Biochemical parameters of peritoneal dialysis patients without and with pulmonary hypertension (PH)

	Without PH (n=21)	With PH (n=15)	p Value
Hemoglobin (g/dL)	10.94±2.48	10.87±1.91	0.93
Albumin (g/dL)	3.32±0.81	3.19±0.56	0.58
Calcium (mg/dL)	9.86±0.98	9.79±0.77	0.82
Phosphorus (mg/dL)	4.56±1.8	5.0±1.8	0.27
Parathyroid hormone (pg/mL)	540±445	569±371	0.84
Ferritin (ng/mL)	873±965	226±210	0.005
Transferrin saturation (%)	15.9±3.5	9.74±2.5	0.85
Lactic dehydrogenase (U/L)	206±79	264±99	0.06
Daily nPCR (g/kg)	0.95±0.27	0.78±0.21	0.049

nPCR = normalized protein catabolic rate.

Discussion

The results of the present study indicate a very high prevalence of PH (42%) on ECHO in our population of PD patients having undergone ECHO for any reason.

To our knowledge, no previous reports regarding the prevalence of PH in PD patients have been published. In a report concerning 3790 ECHO-normal subjects, 28% had a systolic PAP greater than 30 mmHg (13). The recently published literature contains a few papers regarding PH in HD patients. Yigla *et al.* (4) indicated that 39.7% of their HD patients had PH (PAP > 35 mmHg). Amin *et al.* reported a PH prevalence of 29% in HD patients (5), and most recently, Tarass reported 27% (7). We recently reported 75% PH prevalence in our pre-dialysis CKD patients (12), which may in fact reflect pre-existing disease in PD patients.

In the present study of PD patients, only 1 patient had a PAP of 65 mmHg—just short of being termed “severe” PH (PAP > 65 mmHg). In our previously reported pre-dialysis CKD patients (12), 3 (12.5%) had severe PH. Our prevalent HD patients have severe PH prevalence of about 4% [6 of 151 patients by ECHO (8)]. Yigla *et al.* reported severe PH in 28% of the non-ESRD patient population (14).

The lower ferritin levels, higher levels of LDH, lower normalized protein catabolic rate, and higher prevalence of CHF and CAD in our PD patients with PH may contribute to their increased mortality risk. Reports have indicated that PH is prevalent in adult patients with sickle cell disease and is strongly associated with early mortality and markers of hemolysis, in particular serum LDH (15). We previously reported increased mortality risk in HD patients with PH as compared with patients without PH (8), finding that

21% of PH patients and 11% of patients without PH died during the study period. Yigla *et al.* reported 30% and 8.5% mortality rates in patients with and without PH respectively (4). In the present study, however, the difference in mortality between the two groups of PD patients did not reach statistical significance. We could not explain the higher prevalence of PH among continuous cycling PD patients; that finding needs further investigation.

Our finding that PTH correlates directly with PAP in PD patients is interesting. Based on an animal model, Akmal *et al.* suggested that excess PTH in chronic renal failure induces PH, pulmonary calcification, and right ventricular hypertrophy, and proposed that PH develops secondarily to pulmonary artery calcification. Prevention of pulmonary artery

calcification by parathyroidectomy in dogs with CRF was associated with normalization of mean PAP and reduction of right ventricular hypertrophy (11). But Amin *et al.* could not find any statistically significant difference in PTH between 15 patients with PH and 36 patients without PH who were on HD (5).

Conclusions

The present study demonstrates that PH is highly prevalent in PD patients and may be associated with higher mortality risk. The PH in our patients probably reflects a complication of left-chamber heart disease. The association of hyperparathyroidism with PH in PD patients is consistent with our findings in prevalent HD patients (8). This link needs to be confirmed and prospectively explored, especially given the prevalence of secondary hyperparathyroidism, the large number of PD patients with PH, and the excess mortality risk seen with PH in this population. Early diagnosis may enable timely intervention. Considering the limitations of our small number of patients in a retrospective study, these findings need to be further explored in larger prospective studies.

Acknowledgments

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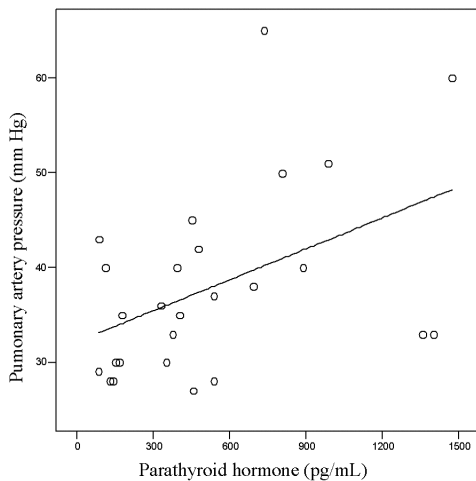


FIGURE 1 Correlation of pulmonary artery pressure with parathyroid hormone. Correlation coefficient: $r = 0.42$; $p = 0.03$.

TABLE III Echocardiography characteristics of peritoneal dialysis patients without and with pulmonary hypertension (PH)

	Without PH (n=21)	With PH (n=15)	p Value
Ejection fraction (%)	56.5±11.8	46.3±19.8	0.07
Left ventricular hypertrophy (%)	43	67	0.16
Diastolic dysfunction (%)	48	33	0.39
Dilated left ventricular chamber (%)	19	53	0.03
Right ventricular dilatation (%)	4.8	13.3	0.56
Mitral valve calcification (%)	29	20	0.70
Global hypokinesia (%)	29	60	0.059

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