ORIGINAL RESEARCH

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Pulmonary hypertension in end-stage renal disease patients on dialysis and pre-dialysis patients

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Abstract

Purpose: Pulmonary hypertension (PH) is a frequent and serious cardiovascular complication in patients with end-stage renal disease (ESRD) on dialysis. The purpose of this study was to investigate the prevalence of PH and its associated factors in patients with ESRD on maintenance dialysis and pre-dialysis patients.

Methods: The medical records of ESRD patients who underwent kidney transplantation between January 2011 and December 2017 were retrospectively reviewed. Demographic and clinical characteristics including echocardiographic findings before joining the waiting list for transplantation were evaluated and compared among groups divided according to dialysis or not and dialysis types. The results of transthoracic Doppler echocardiography were used to determine the pulmonary artery pressure. Pulmonary hypertension was defined as a systolic pulmonary artery pressure (sPAP) greater than 35 mmHg. Univariate and multivariate analyses were used to investigate factors associated with PH.

Results: Data from 35 pre-dialysis patients with ESRD, 72 maintenance hemodialysis (HD) and 34 peritoneal dialysis (PD) patients were analysed. Pulmonary hypertension was 17.1% in pre-dialysis patients, 16.7% in HD patients and 14.7% in PD patients ($P=0.957$). There were negative correlations between sPAP and calcium ($r=-0.230$, $P=0.012$), $\text{Ca} \times \text{P}$ ($r=-0.210$, $P=0.021$), hemoglobin ($r=-0.243$, $P=0.008$) and a positive correlation between sPAP and cardiac output ($r=0.481$, $P=0.000$). Cardiac output (CO) was an independent risk factor of sPAP ($B=1.431$, confidence interval [CI] 95%: 0.687 to 2.175, $P=0.000$).

Conclusion: Incidence of PH was not statistically different in ESRD patients on dialysis and pre-dialysis patients. Uremia may play a major role in the pathogenesis of PH in patients.

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Introduction

Cardiovascular diseases are the major cause of morbidity and mortality in end-stage renal disease (ESRD) patients [1-3]. Pulmonary hypertension (PH), as a serious and progressive cardiovascular complication, is newly recognized in patients with chronic kidney disease [4,5]. Previous studies showed that PH occurred with a frequency of 18.8% to 68.8% in patients receiving chronic hemodialysis (HD) and 0 to 42% in patients on continuous peritoneal dialysis (PD) [6]. It has been demonstrated that PH, either pre-existing before initiating HD or developing incidentally after regular HD treatment, is related to increased mortality rates [2,3,7]. In addition, PH at the start of PD was found to be associated with increased risk of both all-cause and cardiovascular mortality in incident PD patients [8]. Further, elevated pulmonary artery pressure (PAP) complicated or prevented kidney transplant by conferring an increased risk of early graft dysfunction and long-term mortality [9,10]. However, previous studies have mainly focused on dialysis patients. Previous studies regarding unexplained PH in pre-dialysis patients with ESRD are limited, and risk factors promoting PH remain controversial. In this study, we investigated the prevalence of this complication among ESRD patients on HD, PD and in pre-dialysis patients. We also examined potential risk factors through a detailed analysis of clinical data, laboratory indices and echocardiographic data.

Methods

Patients

Data from patients with established ESRD, who underwent kidney transplantation at the 1st Affiliated Hospital of Wenzhou Medical University between January 2011 and December 2017, were retrieved from our database. Patients who received transplants from the prison system were excluded to avoid ethical and legal issues. The medical records of the patients before they joined the waiting list for transplantation were retrospectively reviewed. Clinical characteristics and laboratory parameters were compared among patients on HD, PD and pre-dialysis patients. Patients with a history of congenital cardiac anomalies, chronic obstructive pulmonary diseases, collagen vascular diseases or renal transplants, or who were younger than 18 years of age were excluded from the study. This study was approved by the institutional review board of the 1st Affiliated Hospital of Wenzhou Medical University and was in accordance with the 1975 Helsinki Declaration. Written informed consent was obtained from all patients.

Clinical and laboratory parameters

Clinical data were gathered, including age, gender, height, body weight, type and duration of dialysis. Laboratory indices were recorded, including the serum levels of creatinine, blood urea nitrogen, calcium, phosphorus, parathyroid hormone, albumin, and hemoglobin. The body mass index (BMI) and calcium-phosphorus product ($\text{Ca} \times \text{P}$) was calculated.

Echocardiography

Results of complete transthoracic Doppler echocardiography, which was essential for the evaluation of transplant candidates in our center, were analysed. Systolic PAP (sPAP) was calculated using the modified Bernoulli equation:

$\text{PAP} = 4 \times (\text{tricuspid systolic jet})^2 + 10 \text{ mmHg}$ (estimated right atrial pressure).

Because echocardiographic criteria were used, PH was defined as an estimated sPAP higher than 35 mmHg at rest, which can provide a linear estimate of mean pulmonary artery pressure.

Statistical analysis

Data analyses were performed using the Statistical Package for Social Sciences (SPSS), Version 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Comparisons between groups were performed using the one-way ANOVA. The chi square test was used to compare proportions in different groups. Univariate and multivariate analyses were performed to investigate factors associated with sPAP. A P -value < 0.05 was considered statistically significant.

Results

Data from a total of 164 patients with ESRD who received kidney transplants from living donors or donation after citizen death in our center between 2011 and 2017 were retrieved from the database. Twenty-three patients were excluded because of lack of echocardiographic data or because the echocardiogram was not performed just after dialysis. Thus, data from 141 patients were analysed, including 35 pre-dialysis patients, 72 HD patients and 34 PD patients. The demographic data and clinical characteristics of different groups are presented in Table 1. Patients among the three groups were comparable with regard to age, gender and BMI. There was no difference regarding the duration of dialysis between HD and PD patients. Albumin, creatinine, calcium and hemoglobin levels were different for patients in the three groups (see Table 1). According to the echocardiographic findings, the

mean sPAP was 31.11 ± 6.13 mmHg in pre-dialysis patients, 31.78 ± 6.21 mmHg in HD patients and 30.09 ± 5.05 mmHg in PD patients ($P=0.393$). Pulmonary hypertension

was prevalent in 17.1% of pre-dialysis patients, 16.7% of HD patients and 14.7% of PD patients ($P=0.957$).

TABLE 1. Patients' demographic data and clinical characteristics

Patients' data	Pre-D (n=35)	HD (n=72)	PD (n=34)	P
Age (years)	43.34 $\pm$ 12.52	39.86 $\pm$ 11.87	38.44 $\pm$ 12.86	0.225
Male/female	22/13	50/22	22/12	0.764
BMI (kg/m ²)	20.66 $\pm$ 2.30	20.91 $\pm$ 3.20	21.52 $\pm$ 2.78	0.448
DD (month)	-	23.84 $\pm$ 21.09	23.74 $\pm$ 22.52	0.982
Hypertension	77.14%	76.39%	79.41%	0.941
Antihypertensive				
1 type	33.33%	49.09%	29.63%	0.180
2 types	40.74%	27.27%	25.93%	
3 or more types	25.93%	23.64%	44.44%	
sPAP (mmHg)	31.11 $\pm$ 6.13	31.78 $\pm$ 6.21	30.09 $\pm$ 5.05	0.393
PH	17.1%	16.7%	14.7%	0.957
CO (ml/min)	6.69 $\pm$ 1.64	6.00 $\pm$ 1.68	6.32 $\pm$ 1.82	0.327
LVEF (%)	67.47 $\pm$ 10.82	63.76 $\pm$ 7.22	65.96 $\pm$ 6.66	0.14
Albumin (g/L)	37.87 $\pm$ 4.60	41.62 $\pm$ 4.10	35.92 $\pm$ 6.01	0.00
BUN (mmol/L)	30.53 $\pm$ 18.31	19.26 $\pm$ 7.00	20.24 $\pm$ 7.48	0.077
Creatinine (μ mol/L)	867.87 $\pm$ 359.66	836.01 $\pm$ 214.49	1055.06 $\pm$ 357.43	0.01
Calcium (mmol/L)	1.91 $\pm$ 0.35	2.27 $\pm$ 0.18	2.29 $\pm$ 0.24	0.002
Phosphorus (mmol/L)	1.91 $\pm$ 0.74	1.67 $\pm$ 0.47	1.65 $\pm$ 0.47	0.477
Ca $\times$ P (mg ² /dl ²)	42.66 $\pm$ 10.79	45.01 $\pm$ 16.37	47.24 $\pm$ 15.75	0.617
Parathyroid hormone (pg/ml)	414.87 $\pm$ 246.63	409.52 $\pm$ 466.06	286.40 $\pm$ 311.91	0.393
Hemoglobin (g/L)	84.07 $\pm$ 21.43	107.10 $\pm$ 19.33	94.71 $\pm$ 17.10	0.00

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; Ca $\times$ P, calcium-phosphorus product; DD, duration of dialysis; PH, pulmonary hypertension; sPAP, systolic pulmonary artery pressure

Univariate analysis showed that there were negative correlations between sPAP and calcium ($r=-0.230$, $P=0.012$), Ca $\times$ P ($r=-0.210$, $P=0.021$), hemoglobin ($r=-0.243$, $P=0.008$) and a positive correlation between sPAP and cardiac output (CO) ($r=0.481$, $P=0.000$). Univariate analyses of factors associated with sPAP are presented in Table 2. With multivariate linear regression analysis, CO ($B=1.431$, confidence interval [CI] 95%: 0.687 to 2.175, $P=0.000$) was found to be an independent risk

factor of sPAP. The association between creatinine ($B=-0.001$, confidence interval [CI] 95%: -0.007 to 0.004, $P=0.562$), being on HD ($B=3.246$, confidence interval [CI] 95%: -0.138 to 6.630, $P=0.060$), Ca $\times$ P ($B=-0.684$, confidence interval [CI] 95%: -1.760 to 0.393, $P=0.210$), hemoglobin ($B=-0.050$, confidence interval [CI] 95%: -0.119 to 0.018, $P=0.144$), albumin ($B=-0.192$, confidence interval [CI] 95%: -0.461 to 0.077, $P=0.160$) and sPAP was not significant.

TABLE 2. Univariate analyses of factors associated with sPAP

Factors associated with sPAP	r	p
Creatinine	-0.087	0.343
BUN	0.038	0.683
Calcium	-0.230	0.012
Phosphorus	-0.151	0.103
Ca×P	-0.210	0.021
PH	0.032	0.755
BMI	0.056	0.543
CO	0.481	0.000
Hemoglobin	-0.243	0.008
Albumin	-0.18	0.052
Type of dialysis	-0.157	0.086
DD	-0.144	0.116
LVEF	-0.060	0.517

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; Ca×P, calcium-phosphorus product; CO, cardiac output; DD, duration of dialysis; LVEF, left ventricular ejection fraction; PH, pulmonary hypertension; sPAP, systolic pulmonary artery pressure

Discussion

In this study, we investigated the prevalence of PH in ESRD patients waiting for kidney transplantation with or without dialysis and found it was comparable among groups. The syndrome of PH in ESRD patients was initially described among patients receiving HD therapy, and was largely attributed to arterio-venous fistula-mediated elevated cardiac output [11,12]. Recent studies have begun to focus on patients undergoing PD. It has been generally considered that PH was more frequent in patients undergoing HD than in patients undergoing PD. Bozbas et al. reported a PH ratio of 18.8% in HD patients compared with 5.9% in PD patients [13]. Etemadia et al. reported results (41.1% vs. 18.7%) consistent with those of Bozbas et al. [14]. In contrast, Zhang et al. found no difference in PH between HD and PD patients (37.5% vs. 31.8%) [15]. Our present study also found that the prevalence of PH was comparable in patients on HD (16.7%) and PD (14.7%) and even higher in pre-dialysis patients (17.1%) although the difference was not significant.

The pathogenesis of PH in ESRD patients has not been completely elucidated and the mechanisms leading to the disease are still under investigation. Elevated pulmonary blood flow and an increased pulmonary vascular resistance are the two main mechanisms described in the development of PH. Fluid overload is a common complication among ESRD patients [16]. A recent study, using multifrequency bioimpedance analysis to assess fluid status in HD patients, demonstrated a strong relationship between fluid overload and PH. It also found that, in step with the decrease of overhydration/extracellular water ratio (12.40 ± 2.35 vs. 5.13 ± 1.72), which is an indicator of fluid status, sPAP was significantly reduced after HD (37.14 ± 13.26 vs. 31.02 ± 11.36) [17]. Our study demonstrated that CO was an independent predictor of PH. As echocardiograms were routinely performed just after HD, when excess fluid was removed by ultrafiltration, our study showed sPAP was comparable in pre-dialysis and HD patients (who usually had arterio-venous fistula, which can contribute to the development of PH by increasing CO) [14,18]. Furthermore, our study confirmed anemia, which may aggravate hypoxia and increase CO in patients with ESRD as a risk factor of PH, by univariate though not multivariate analysis.

With regard to pulmonary vascular resistance, it is accepted that the changes in anatomy or function of pulmonary vessels result in the inability of the pulmonary circulation to maintain elevated CO, which may cause PH. Some studies have focused on dysregulation of calcium/phosphorus metabolism in patients with ESRD, which can lead to pulmonary vascular calcification and increased resistance [19]. Our present study showed that sPAP was negatively correlated with serum levels of calcium and Ca×P. In contrast, a study by Etemadi et al. did not reveal any significant association between calcium/phosphorus metabolism and PH in ESRD patients [14].

This study had a number of limitations. The retrospective observational design of the study and the small sample size were obvious limitations. In addition, PAP was measured by non-invasive Doppler echocardiography, which can both under- and overestimate pulmonary pressure due to technical limitations and cannot discriminate between pre- and post-capillary PH [20].

In conclusion, in our retrospective study group, PH was not observed more frequently in ESRD patients on dialysis than in pre-dialysis patients. Uremia, with its associated fluid overload, anemia and dysregulation of calcium/phosphorus metabolism, may all play a major role in the pathogenesis of PH in patients.

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