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TANAFFOS

Contributing Factors of Pulmonary Hypertension in Hemodialysis Patients

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Background: Pulmonary hypertension (PH) is a known complication of hemodialysis (HD) but its pathogenesis and etiology is not completely clear. The purpose of the current study is to determine the prevalence and possible causes of PH among hemodialysis patients.

Material and Methods: Demographic, clinical and laboratory data of 40 patients referred to hemodialysis ward of Masih Daneshvari Hospital during 12 months were recorded. Detailed echocardiography was performed for each patient within 24 hours of hemodialysis. PH was defined as systolic pulmonary artery pressure (SPAP) above 35 mmHg.

Results: 12 of 40 HD patients had PH (prevalence = 30%). The hemodialysis vintage in PH group was longer than patients without PH (No PH group) . Also, left atrium size, right ventricle size, left ventricle end diastolic diameter (LVEDD) and left ventricular mass index (LV mass index) were significantly higher in PH group; but ejection fraction (EF) was lower than No PH group. Left ventricle diastolic dysfunction and pericardial effusion were significantly associated with PH. The crude mortality rate was relatively similar in PH group and No PH group.

Conclusion: PH is prevalent in HD patients with multifactorial etiology. Increased pulmonary capillary wedge pressure (PCWP) is a very important factor to induce PH in these patients; on the other hand, chronic volume overload and left ventricle systolic and diastolic dysfunction are some of the predominant causes of increased PCWP in this population.

Keywords: Hemodialysis; Pulmonary hypertension; Echocardiography

INTRODUCTION

In the simplest sense, PH is defined as any increased pulmonary artery pressure from its normal level (the upper limit of normal mean pulmonary artery pressure is 19 mmHg) (1). Currently, PH is identified as a common complication of chronic kidney disease (CKD) and end-stage renal disease (ESRD) while its prevalence in hemodialysis patients is estimated between 27 to 58% in different studies (2-14). The pathogenesis and possible causes of PH in hemodialysis patients is not completely known. Some possible etiologies include increased cardiac output (CO), increased pulmonary vascular resistance (PVR), increased PCWP (10, 15); anemia (3, 6, 9, 10, 16), volume overload (3, 10), arterio-venous AV- fistula (3, 8, 10 and 17), uremia and endothelial dysfunction (16, 18) in addition to vascular calcification, increased PTH (3, 18- 20), recurrent thrombo-emboli (21), congestive heart failure (22), and diastolic dysfunction (23). However, it is worth noting that some studies show that the mentioned factors do not induce PH in hemodialysis patients (9, 12, 16, 18, 19, 23-28). Although echocardiography is not a gold standard technique like right heart catheterization in accurate

measurements of PH (1), it is reliable as a screening tool for estimation and evaluation because of its low cost, non-invasive nature, ease of use, and its availability (29). Regardless of the mechanism of the PH in hemodialysis, PH is involved in the outcome of kidney transplantation of these patients (30) in addition to increased morbidity and mortality due to right ventricle dysfunction (1, 10). There is strong evidence suggesting PH as a strong independent factor affecting mortality rate in hemodialysis patients (31). Thus, according to the importance of identifying increased pulmonary artery pressure (PAP) and also several differences in terms of associated causes of PH in patients with renal failure, accurate assessment of PH in CKD and ESRD, especially in hemodialysis patients is very important. Before the treatment, the background etiology of PH should be clearly specified (22) because useful treatments for some types of pulmonary artery hypertension may be harmful for other types (1).

The purpose of the present study is to determine the prevalence of PH among hemodialysis patients referred to Masih Daneshvari Hospital as a tertiary center, the one-year mortality rate, and possible causes of developing PH in the mentioned population.

MATERIALS AND METHODS

The present study is an analytical prospective study that was done in the hemodialysis ward of Masih Daneshvari Hospital in Tehran. Echocardiography was performed for 40 patients with ESRD who were undergoing hemodialysis in this center, regardless of age, gender, ESRD cause, and venous route type. Patients with chronic pulmonary disease, positive history of pulmonary thrombo-emboli (PTE), positive HIV test, and patients whose dialysis vintage was less than one month were excluded from the study. Demographic, clinical, and laboratory data were recorded using medical records of patients. All the laboratory data were done during a week before echocardiography. All the echocardiographies were performed within 24 hours after hemodialysis when the patient had reached the dry weight which was determined based on the physical examination by nephrologists. All echocardiographies were performed by an experienced echocardiographer with a Vivid- 7 Dimension Echo machine (GE, Norway), probe frequency 2.5 MHZ. The evaluation included two-dimensional, M.mode Doppler, and tissue Doppler echocardiography. Systolic PAP, ejection fraction, fistula diameter, and blood flow of AVF and also the grade of diastolic dysfunction, ventricular filling pressure (estimated with E/E` ratio), right ventricle size and function, left atrium enlargement and left ventricular hypertrophy were assessed for each patient based on the guideline prepared by the American Society of Echocardiography (ASE) (32, 33). Systolic PAP was calculated by a modified equation of Bernoulli (32) and values greater than 35 mm Hg indicated pulmonary hypertension (PH). Accordingly, hemodialysis patients were divided into two groups including “PH” and “non-PH” patients. Patients were checked for any known risk factor or echocardiographic parameter which is usually suggested as a causative factor and were compared for them regarding PH absence or existence.

Statistics

Categorical variables were expressed by percentages using the Chi-square test or similar ones. According to the type of variables, comparing two groups was performed using “Student’s T-test”, “Pearson correlation coefficient”, and “Chi-square test” or “Mann Whitney u test” (if abnormally distributed). All the analyses were performed using the Statistical Package of Social Science version 20. P-value less than 0.05 ($P < 0.05$) was considered statistically significant with a 95% confidence interval and type one error=0.05.

Ethics

Participants were informed of the purpose and design of the investigation and signed an appropriate written informed consent form. The research protocol was approved by the Ethics Committee in Research of Shahid Beheshti University of Medical Sciences.

RESULTS

Clinical data in patients with and without PH is shown in Table 1. Laboratory data of all patients and also subgroups of PH and non-PH is shown in Table 2. There was no statistically significant difference between the two groups regarding laboratory findings.

The echocardiographic findings of patients are shown in Table 3. The mean SPAP of all the patients was 35±12 mmHg (50±13 and 29±3 mmHg, in the PH group and non-PH group, respectively). The right ventricle size was larger in the PH group (3.5±0.6 vs. 2.9±0.4 cm; P=0.03). Mean Left ventricle EF was 47.4±10.6% in all patients and was significantly lower in the PH group than non-PH (42.2±13.5 vs. 49.6±8.5%; P=0.04). Left ventricle filling pressure estimation (E/E' ratio) was significantly higher in the PH group (20.8±5.2 vs. 10.8±4.3; P=0.00) and accordingly, left atrium size and left ventricle end-diastolic diameter were greater in PH group compared to non-PH group (P<0.05). Diastolic dysfunction (grade II and III) with Pearson's coefficient of 0.03 was associated with PH. Pericardial effusion was much more common in the PH than non-PH group (41 vs. 3%; P=0.02).

In the 12-month follow-up period, two of 12 patients with PH and four out of 28 non-PH patients died (crude mortality rate was 16 and 14%, respectively).

Some of the demographics as well as clinical, laboratory, and echocardiographic data of died patients in comparison with alive patients are shown in Table 4. Died patients had a higher mean of age (67±8.1 vs. 50.9±16.3 years; P=0.02). Five of the six dead patients had ischemic heart disease (p=0.01). There was no significant correlation between EF, SPAP, and diastolic dysfunction and mortality.

Table 1. Clinical data in patients with and without PH

Variables		PAP > 35	PAP ≤ 35	All	P
Prevalence n (%)		12 (30%)	28 (70%)	40 (100%)	-
Age (year)		52.5 ± 14.1	53.7 ± 17.5	53.3 ± 16.4	0.84
Male / female (n)		8 / 4	14 / 14	22 / 18	0.33
Etiology of ESRD n (%)	DM	4 (33%)	14 (50%)	18 (45%)	0.39
	HTN	1 (8%)	1 (3%)	2 (5%)	
	ADPKD	2 (16%)	2 (7%)	4 (10%)	
	CVD	0 (0%)	5 (17%)	5 (12%)	
	Others	2 (16%)	3 (10%)	5 (12%)	
	Unknown	3 (25%)	3 (10%)	6 (15%)	
Duration of HD in week (hrs)		12.2 ± 2.5	10.9 ± 1.8	11.3 ± 2.1	0.06
Dialysis vintage (months)		41.0 ± 35.9	23.3 ± 18.6	28.6 ± 25.9	0.04
Dialysis access n (%)	AVF	8 (66%)	16 (57%)	24 (60%)	0.57
	Catheter	4 (33%)	12 (42%)	16 (40%)	
Number of AVF		1.16 ± 0.57	0.75 ± 0.64	0.87 ± 0.64	0.06
Site of AVF n (%)	Brachial vein	6 (75%)	12 (75%)	18 (75%)	1.00
	Radial vein	2 (25%)	4 (25%)	6 (25%)	
Erythropoietin usage (IU/week)		10000 ± 4670	8928 ± 4973	9250 ± 4850	0.52
Underlying disease	IHD	5 (41%)	8 (28%)	13 (32%)	0.42
	CVD	0 (0%)	3 (10%)	3 (7%)	
Mortality n (%)		2 (16%)	4 (14%)	6 (15%)	0.84

Abbreviations: PH, pulmonary hypertension; DM, diabetes mellitus; HTN, hypertension; ADPKD, autosomal dominant polycystic kidney disease; CVD, collagen vascular disease; HD, hemodialysis; AVF, arteriovenous fistula; IHD, ischemic heart disease.

Table 2. Laboratory data in patients with and without PH

Variables	PAP > 35	PAP ≤ 35	All	P
IPTH (pg/ml)	416.5 ± 361.1	314.3 ± 400.9	345.0 ± 387.7	0.45
Serum Iron (µg/dl)	61.4 ± 32.9	52.2 ± 25.3	55.0 ± 27.7	0.34
SI/TIBC (%)	15.5 ± 7.2	15.7 ± 7.7	15.7 ± 7.5	0.93
Hemoglobin (g/dl)	10.4 ± 1.4	10.6 ± 1.9	10.5 ± 1.8	0.74
KT/V*	1.11 ± 0.25	1.16 ± 0.29	1.15 ± 0.2	0.58
Albumin (g/dl)	3.6 ± 0.2	3.5 ± 0.5	3.5 ± 0.4	0.36
Calcium (mg/dl)	8.2 ± 0.4	8.1 ± 0.7	8.1 ± 0.6	0.58
Phosphorus (mg/dl)	5.5 ± 1.1	5.6 ± 1.8	5.6 ± 1.6	0.88

Abbreviations: PH, pulmonary hypertension; IPTH, intact parathyroid hormone; SI, serum iron; TIBC, total iron binding capacity.

* K, dialyzer clearance of urea; t, dialysis time; V, volume of distribution of urea. Kt/V was calculated using the Daugirdas JT. Formula (34).

Table 3. Echocardiographic data in patients with and without PH

Variables		PAP > 35	PAP ≤ 35	All	P
SPAP (mmHg)		50.1 ± 13.8	29.7 ± 3.0	35.6 ± 12.2	-
PAT < 100ms n (%)		8 (66%)	5 (17%)	13 (32%)	0.03
EF (%)		42.2 ± 13.5	49.6 ± 8.5	47.4 ± 10.6	0.04
AVF flow (ml/min)		3144.4 ± 2870.7	2437.5 ± 2560.6	2643.7 ± 2611.3	0.55
Diameter of AVF (cm)		0.8 ± 0.1	0.7 ± 0.2	0.7 ± 0.2	0.40
RV size (cm)		3.5 ± 0.6	2.9 ± 0.4	3.1 ± 0.6	0.03
LA size (cm)		4.0 ± 0.7	3.5 ± 0.7	3.6 ± 0.8	0.04
LA area (cm2)		23.3 ± 4.9	19.2 ± 6.3	20.4 ± 6.2	0.05
LVH n (%)		7 (58%)	10 (35%)	17 (42%)	0.18
DD	**NL and grade I**	3 (25%)	21 (75%)	24 (60%)	0.03
	Grade ≥ II	9 (75%)	7 (25%)	16 (40%)	
Moderate to severe MR		4 (33%)	2 (7%)	6 (15%)	0.03
LV mass (gram)		258.7 ± 67.8	185.6 ± 78.6	204.9 ± 81.8	0.01
TAPSE (mm)		21.8 ± 5.6	21.3 ± 3.3	21.4 ± 4.0	0.76
TASV (cm/s)		11.6 ± 3.2	13.3 ± 3.6	12.9 ± 3.5	0.22
RV MPI		0.57 ± 0.09	0.68 ± 0.24	0.66 ± 0.21	0.24
LV MPI		0.52 ± 0.15	0.59 ± 0.17	0.58 ± 0.17	0.48
E/E' ratio		20.8 ± 5.2	10.8 ± 4.3	13.1 ± 6.1	0.00
LVEDD (cm)		5.8 ± 0.6	5.2 ± 0.8	5.4 ± 0.8	0.05
LVESD (cm)		4.2 ± 0.8	3.6 ± 0.9	3.8 ± 0.9	0.13
PE (%)		5 (41%)	1 (3%)	6 (15%)	0.02

Abbreviations: PH, pulmonary hypertension; SPAP, systolic pulmonary arterial pressure; PAT, pulmonary acceleration time; EF, ejection fraction; AVF, arteriovenous fistula; RV, right ventricle; LA, left atrial; LVH, left ventricular hypertrophy; DD, diastolic dysfunction; NL, normal; MOD, moderate; MR, mitral regurgitation; LV, left ventricle; TAPSE, tricuspid annular plane systolic excursion; TASV, tricuspid annular systolic velocity; MPI, myocardial performance index; E/E', the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E'); LVEDD, left ventricle end diastolic dimension; LVESD, left ventricle end systolic dimension; PE, pericardial effusion.

Table 4. Distribution of clinical, laboratory and echocardiographic data in the survivors and non-survivors

Variables		Non-survivors	Survivors	P
Prevalence n (%)		6 (15%)	34 (85%)	-
Age (year)		67.0 ± 8.1	50.9 ± 16.3	0.02
Male / female (n)		4 / 2	18 / 16	0.53
Dialysis vintage (months)		35.3 ± 17.4	27.4 ± 27.1	0.50
Etiology of ESRD n (%)	**DM**	4 (66%)	14 (41%)	0.39
	HTN	1 (16%)	1 (2%)	
	ADPKD	0 (0%)	4 (11%)	
	CVD	0 (0%)	5 (14%)	
	Others	0 (0%)	5 (14%)	
	Unknown	1 (16%)	5 (14%)	
Underlying disease	**IHD**	5 (83%)	8 (23%)	0.01
	CVD	0 (0%)	3 (12%)	
Hemoglobin (g/dl)		10.0 ± 1.4	10.6 ± 1.8	0.39
Kt/V*		1.3 ± 0.2	1.12 ± 0.2	0.17
SPAP (mmHg)		34.5 ± 5.1	36.1 ± 13.1	0.77
EF (%)		50.0 ± 9.6	46.9 ± 10.9	0.51
DD grade ≥ II n (%)		3 (50%)	13 (38%)	0.58
LVH n (%)		4 (66%)	13 (38%)	0.19

Abbreviations: DM, diabetes mellitus; HTN, hypertension; ADPKD, autosomal dominant polycystic kidney disease; CVD, collagen vascular disease; IHD, ischemic heart disease; SPAP, systolic pulmonary arterial pressure; EF, ejection fraction; DD, diastolic dysfunction; LVH, left ventricular hypertrophy.

* K, dialyzer clearance of urea; t, dialysis time; V, volume of distribution of urea. Kt/V was calculated using the Daugirdas JT. Formula (34).

DISCUSSION

Currently, PH is identified as a common complication of ESRD and CKD with a wide range of prevalence in hemodialysis patients between 27% and 58% as reported by various studies (2-14). The present study found a 30% frequency for PH among our HD patients. One of the main causes of differently reported prevalences in various studies could refer to hemodialysis vintage in the patients which allows the confounding factors for developing PH. Studies reporting a higher prevalence of PH in HD patients had longer hemodialysis vintage compared to our study. One of the other causes of this difference may be the time taken for echocardiography. Furthermore, SPAP decreased by 7 mmHg through HD (15). In our study, all the patients underwent echocardiography after hemodialysis and almost with their dry weight. Echocardiography of all the patients was performed by a single echocardiologist unrespecting the indications and clinical signs and symptoms.

In our study, levels of hemoglobin, calcium and phosphorus, IPTH, and the dosage of erythropoietin were not associated with PH. In support of this finding, many studies did not find any relationship between these factors and PH (9, 10, 12, 16, 18, 19, 23-27). It is logical that according to health care provided by specialists in HD centers, severe anemia, and severe secondary hyperparathyroidism are less common. On the other hand, due to the long time required for the above-mentioned factors, these factors are not important causes of PH in HD, at least in a short timeframe. Also, in our study, venous route type (AVF vs. central venous catheter), flow, diameter, and fistula location were not correlated with PH. It was not unexpected and many other studies have consistent results (11, 12, 28).

Important parameters in echocardiography had a positive correlation with PH. The larger left atrium and higher left ventricle end-diastolic diameter (EDD) in HD patients with PH is highly suggestive that increased left ventricle filling pressure in HD patients plays an important role in developing PH. One of the important causes of increased PCWP in these patients can be a chronic volume overload. A strongly positive association of pericardial effusion and a higher E/E ratio (high LV end-diastolic pressure) with PH support this idea. In our study, left ventricle diastolic dysfunction was associated with PH; which was in the category of group 2 of PH according to the World Health Organization (WHO) classification which means PH with increased PCWP. In previous studies, the association between diastolic LV dysfunction and PH was shown (23) and this association was also significant in our study. Increased LV mass is associated with systolic and diastolic dysfunction (35) and its association with PH was proven in our study. Regardless of the causes of death, the crude mortality rate was slightly higher in the PH group and five of six dead patients had ischemic heart disease. The cause of the lack of association between PH and mortality in our study was probably a small sample size.

CONCLUSION

According to our study, most cases of PH in HD patients are classified as group 2 of PH. Therefore, any attempt to resolve the chronic volume overload and treat left ventricular systolic and diastolic dysfunction can probably improve PH. As the dialysis vintage is extended, the risk of developing PH in HD patients is increased. So, early kidney transplantation can be a preventive strategy for PH rate reduction in ESRD patients.

Conflict of interest

The authors declare that there was no conflict of interest regarding the publication of this paper throughout the study.

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