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PULMONARY HYPERTENSION IN HEMODIALYSIS PATIENTS

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Abstract

Background: Pulmonary hypertension (PH) in end-stage renal disease (ESRD) patients is associated with significantly increased morbidity and mortality. The prevalence of PH in dialysis patients is relatively high, and varies in different studies from 19% to 70%, depending on the mode of dialysis and other selection factors, such as the presence of other cardiovascular comorbidities.

Methods: This cross-sectional study included 60 chronic hemodialysis patients. Patients with co-morbid conditions and those with a high probability of secondary pulmonary hypertension were excluded. The patient's basic demographics, clinical data, and laboratory results were obtained from hospital records. Trans-thoracic echocardiography including two-dimensional, M-Mode and Doppler studies were performed within 24 hours after the completion of dialysis. Cardiac dimensions and systolic (mild to severe) and diastolic (grades I to III) cardiac dysfunctions were assessed. Study population was divided into two subgroups based on the absence or presence of PH, and parameters were compared using Student's t-test and chi-square tests as indicated.

Results: The study included 24 males (40%) and 36 females (60%). The prevalence of PH was 35%. Patients were subdivided into two groups based on SPAP. The PH group had a statistically significant higher interdialytic weight gain (2.88 ± 1.10 vs. 1.92 ± 0.97, P= 0.010). Echocardiographic measurements showed that PH group had a statistically significantly higher Left Ventricle End Diastolic Volume (LVEDV), Left Ventricle End Systolic Volume (LVESV), Left Atrium (LA) and Aortic root (AR) diameters compared to the normal group, and a significantly lower EF%. SPAP had positive significant correlations with Interdialytic weight gain. Linear regression established that Interdialytic weight gain could statistically significantly predict SPAP.

Conclusions: PH is highly prevalent among patients on HD and it may be associated with mild to moderate impairment of cardiac systolic function. That seems to be related to chronic fluid volume overload and increased interdialytic weight gain. Baseline and regular echocardiographic evaluation of SPAP in patients on HD is recommended. Careful assessment of volume state along with encouraging patients to limit interdialytic weight gain may help reduce SPAP.

Introduction

Cardiovascular disease is a major cause of morbidity and mortality among patients with end-stage renal disease (ESRD). These patients frequently suffer from hypertension and left ventricular hypertrophy, systolic and diastolic cardiac dysfunction, atherosclerosis and coronary artery disease [1]. Pulmonary hypertension (PH) is another severe and progressive cardiac complication that has been recently under attention and frequently seen among ESRD patients. Studies have shown a frequency of about 19% to 70% in patients on chronic hemodialysis (HD) that PH is associated with increased mortality and poor outcomes in these patients [2].

Pulmonary hypertension in CKD

Pulmonary hypertension is a well-recognized complication of chronic kidney disease (CKD). There is significant epidemiological overlap with kidney disease and the underlying causes of PH (pulmonary arteriopathy, left heart disease, chronic pulmonary disease, and chronic thromboembolic disease) [3]. In addition, an entity of unexplained PH in patients with CKD has emerged, with prevalence estimates of 30-50%. The pathogenesis of PH in this population is due to alterations in endothelial function, increased cardiac output, and myocardial dysfunction leading to elevated left heart filling pressure. The mechanism of development of PH in ESRD patients is shown in Fig. 1. Recent data suggest that left heart dysfunction may account for a vast majority of cases of PH in patients with kidney disease. PH is an independent predictor of increased mortality in patients on dialysis and those undergoing kidney transplantation [4]. Pathophysiology of PH in CKD has been attributed to several factors such as, endothelial dysfunction, nitric oxide production, endothelin, Inflammation and oxidative stress and right ventricular failure.

Endothelial dysfunction: Increased cytokines and growth factors – fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), angiotensin converting enzyme (ACE) – lead to abnormal smooth muscle proliferation resulting in arterial myointimal proliferation and fibrosis. The effect of these perturbations and pressure overload lead to worsening PH. Presence of prostaglandins also create imbalance between vasoconstriction and vasodilation which, in turn, affects the PH. Lower levels of pH associated with dimethylarginine inhibit NO production. Reduced NO synthase has potential effects of increased hemoglobin levels [5].

Vascular effects of Endothelin: A schematic diagram of the vascular effects of ET-1 is shown in Fig. 2. ET- 1 is generated in endothelial and smooth muscle cells in response to oxidized LDL, angiotensin II (AngII), etc. The stimulation of endothelial ET_B receptors increases the release of NO, whereas ET_A receptors mediate contraction and cell proliferation and migration. ET-1 stimulates interleukin (IL) and tumor necrosis factor-α (TNF-α) expression in monocytes, leukocyte adherence, platelet aggregation, and adhesion molecule expression. ET-1 stimulates the production and action of growth factors, DNA and protein synthesis, and cell cycle progression. In addition, inflammation, oxidative stress and right ventricular failure also contribute to endothelial dysfunction, leading to PH. Biomarkers of PH include altered ratio of prostacyclin to thromboxane, nitric oxide content in exhaled air, elevated endothelin ET-1/ET-3 ratio, elevation of interleukins, TNF, MCP-1, TGF-β and isoprostanes. Brain natriuretic peptide (BNP) predicts mortality, degree of impairment and response to treatment [5].

An additional mechanism that may underlie the elevated pulmonary arterial pressure (PAP) in HD patients may be hemodynamic changes associated with the placement of arteriovenous fistula (AVF). The increase in cardiac output (CO) due to enhanced venous return to the heart, and subsequent exaggerated pulmonary blood flow may also play a crucial role in the development of PH in HD patients [6,7]. Unusually, the PH in HD patients was found to be almost completely reversible following reduction of CO or amelioration of the uremia, by kidney transplantation or temporary AV compression or surgical ligation of fistula [8]. The number of patients requiring chronic hemodialysis is rapidly growing worldwide. Hemodialysis both greatly reduces quality of life and is associated with extremely high mortality rates. Management of care of patients requiring chronic hemodialysis is complex as it is related to the overall cardiovascular disease burden, blood pressure control, anemia, abnormalities in mineral metabolism, and inflammation. As much as 50% of deaths in maintenance hemodialysis patients are attributable to cardiovascular causes, influenced in part by the development of atherosclerosis and arteriosclerosis, left ventricular hypertrophy (LVH), and sudden cardiac death [9]. PH has been reported as an unrecognized threat in many patients with ESRD [10]. The mortality rate was 30.4% for elevated PAP in HD patient group and 8.5% for the normal PAP group as calculated by Kaplan-Meier survival analysis (p¼ 0.024) [11]. Ramasubbu *et al*. have found that the one-year survival of patients with PH was 74 %, compared with 94 % in patients without PH [12]. Thus, PH plays an important role in predicting CV events and mortality in HD patients [13].

Previous studies on PH are mostly retrospective and are not consistent. Lack of information regarding PH in patients on different types of renal replacement therapies (RRTs), and the scarce use of continuous ambulatory peritoneal dialysis (CAPD) in Egypt necessitate investigation of PH and associated factors among such patients [14]. The main objective of the present study is to estimate the prevalence of PH and associated risk factors among chronic HD patients.

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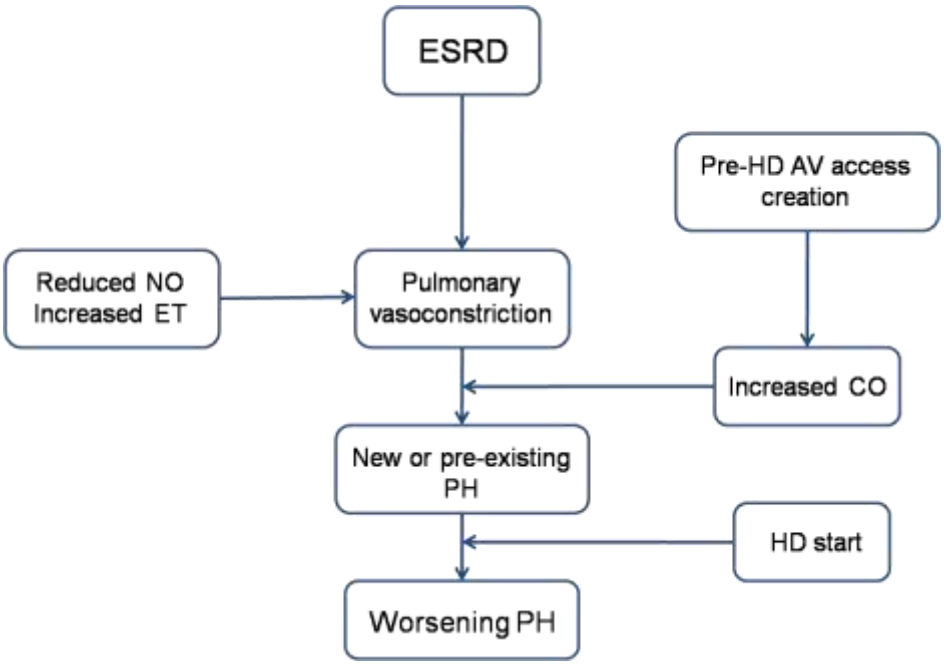


Figure 1: ***Mechanism of development of pulmonary hypertension in ESRD patients (Adapted from Schulman et al., 2013, Ref.5)***

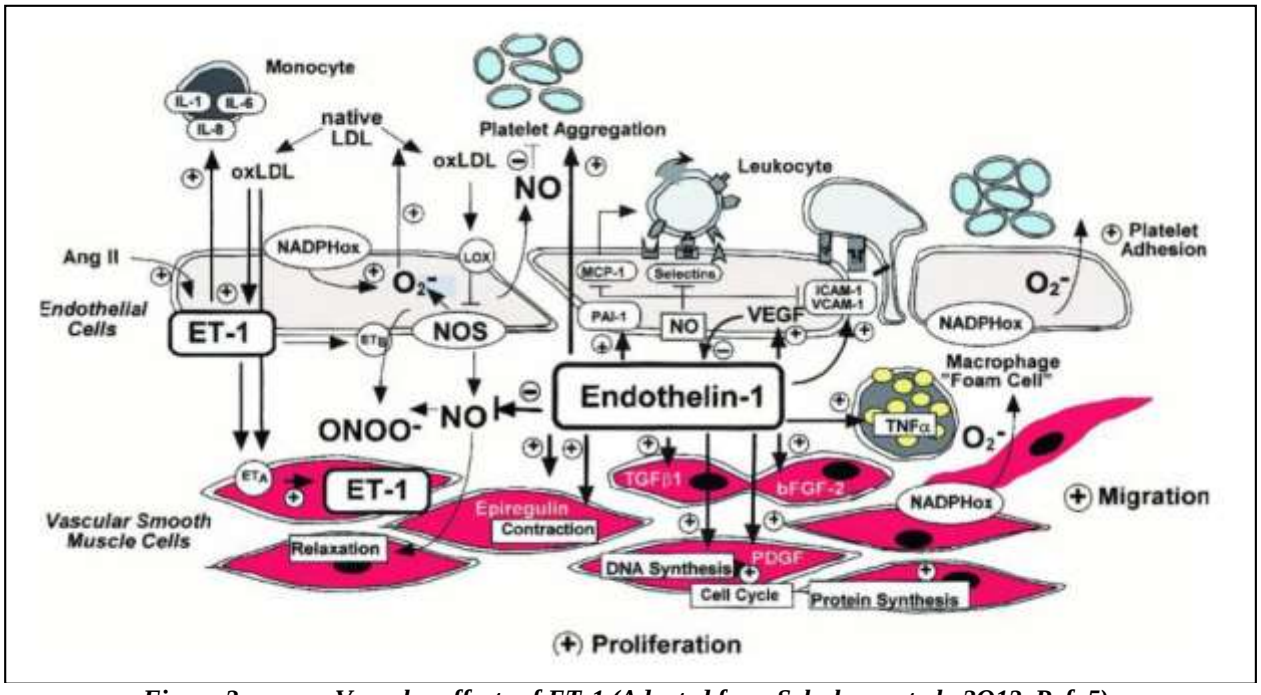


Figure 2: ***Vascular effects of ET-1 (Adapted from Schulman et al., 2013, Ref. 5)***

Materials and methods

This study included 60 chronic hemodialysis patients recruited from Ain Shams University Hospital, Cairo, Egypt. Patients with co-morbid conditions and those with a high probability of secondary pulmonary hypertension were excluded.

Patient assessment

Basic demographics (including age and gender) and data regarding the kidney disease and vascular access were obtained from patients' hospital records. Pre- and post-dialysis blood pressure (BP) recorded were averaged over two weeks. Blood tests for hemoglobin, hematocrit, calcium, phosphorus, parathyroid hormone, albumin, creatinine, blood urea nitrogen and cholesterol post-dialysis levels were sampled at the, within 1 week of the echocardiography study. The mean of the six monthly lab test values preceding the echocardiography study as well as the results of the pre-dialysis blood samples at time of the echocardiographic study were utilized. Patients with SPAP >40 mm Hg were further evaluated in order to uncover other potential causes of PH. This assessment included history, physical examination and chest radiogram.

Echocardiograms and estimation of systolic pulmonary artery pressure (SPAP)

Echocardiography was performed within 24 hours after the completion of dialysis while the patients were at optimal dry weight according to clinical volume status assessment, including BP and weight, to avoid over-estimation of systolic pulmonary artery pressure (SPAP) due to volume overload occurs between the dialysis sessions.

Two-dimensional, M-mode, and Doppler echocardiography exams were performed on all of the participants by a single experienced echocardiographer dedicated to this study. A General Electric Vivid 7 Pro cardiac ultrasound machine (General Electric, Horten, Norway), equipped with a 2.5 MHz phased array probe was used. Cardiac dimensions and systolic (mild to severe) and diastolic (grades I to III) cardiac dysfunctions were assessed according to the guidelines of the American Society of Echocardiography. Left ventricular ejection fraction was estimated from 2-D-derived M-mode linear measurements, using the method described by Teichholz et al. [15]. Evaluation of left ventricular diastolic function Mitral E peak deceleration time was measured from the mitral inflow velocity envelope (obtained by pulsed-wave Doppler examination with a sample volume of 2.0 mm placed at the tips of the mitral valve leaflets). Isovolumetric relaxation time (defined as the time interval from the end of aortic systolic outflow to the onset of mitral inflow) was estimated by placing the sample volume in the LV outflow tract close to the anterior mitral leaflet, in order to record both inflow and outflow signals simultaneously. The Doppler sample volume was placed at the medial mitral annulus and the early mitral annular (medial) diastolic velocity (e') was measured (cm/s).

As for SPAP estimation, multiple views using different acoustic windows were obtained to measure the most optimal tricuspid regurgitation (TR) jet signal using continuous wave (CW) Doppler at a sweep speed of 100 to 200 mm/s. Only CW signals that demonstrated the peak velocity of the TR jet were used for this analysis. SPAP was estimated based on the modified Bernoulli equation as follows (16): 4 V2 (V = peak velocity of TR in meters per second, obtained using the CW Doppler) was added to the estimated right atrial pressure (RAP). The RAP was estimated based on the dimensions of the inferior vena cava (IVC) during inspiration. The RAP was estimated to be 5 mmHg if the IVC size was less than 2.0 cm and collapsed by 50% during inspiration, 10 mmHg if the IVC was less than 2.0 cm and did not collapse by 50%, 15 mmHg if the IVC was greater than or equal to 2.0 cm and collapsed more than 50%, and 20 mmHg if the IVC was greater than or equal to 2.0 cm and did not collapse by 50%. A patient was considered to have PH if the SPAP was greater than or equal to 40 mmHg (17). All of the studies were evaluated off line by an experienced echocardiographer who was blinded to the patients' clinical data.

Statistical analysis

Mean values and standard deviations were used to describe the quantitative variables. Numbers and percentages were used to describe the categorical variables. Student's *t*-test for independent samples was applied to compare the mean values of continuous variables. Chi-square statistics were used to assess the differences between proportions. Pearson's Correlation and Linear regression were utilized. A two-sided P value <0.05 was considered statistically significant. Statistical analyses were performed using Statistical Package (SPSS, version 20.0; SPSS Inc., Chicago, IL, USA).

Results

The patient population consisted of 24 males (40%) and 36 females (60%)**.** Basic patient demographics and clinical characteristics are listed in (Table 1).

The prevalence of PH in our study was estimated at 35%. Patients were subdivided into two groups based on their estimated SPAP: Group A consisted of 39 patients with normal SPAP, and Group B consisted of 21 patients with high SPAP. A comparison of the demographic and clinical characteristics of the two groups is shown in (Table 2). The PH group (Group B) had a statistically significant higher interdialytic weight gain (2.88 ± 1.10 vs. 1.92 ± 0.97, P= 0.010) compared to group A.

On the basis of echocardiography measurements shown in (Table 3), it was observed that the PH group (Group B) had a statistically significantly higher Left Ventricle End Diastolic Volume (LVEDV), Left Ventricle End Systolic Volume (LVESV), Left Atrium (LA) and Aortic root (AR) diameters compared to the normal group (Group A) (LVEDV 5.44 ± 0.56 vs. 5.08 ± 0.79, *P* = 0,645; LVESV 3.92 ± 0.72 vs. 3.37 ± 0.81, *P* = 0.802; LA 3.75 ± 0.82 vs. 3.43 ± 0.59, P = 0.018; AR 3.29 ± 0.34 vs. 3.13 ± 0.52, *P* = 0.21). Also, Group B had a significantly lower EF% compared to Group A (54.75 ± 10.46 vs. 62.47 ± 7.49, *P* = 0.003). Group B patients had a higher degree of diastolic dysfunction compared to the normal group, but the difference was not significant.

As shown in Table 4, SPAP had positive significant correlations with Interdialytic weight gain (r = 0.348, P = 0.007) as well as an inverse significant correlation with EF% (r = -0.413, *P* = 0.001). The correlations of SPAP with Interdialytic weight gain are shown in Fig. 3. To determine whether Interdialytic weight gain can predict the development of PH, linear regression analysis was performed. Linear regression established that Interdialytic weight gain could statistically significantly predict SPAP, F(1, 58) = 5.521, p = 0.022 (Table 5) and Interdialytic weight gain accounted for 8.7% of the explained variability in SPAP (Table 6). The regression equation was: predicted SPAP = 28.66 + (3.19 x Interdialytic weight gain).

Table 1: Categorical demographic and clinical Characteristics of the study Population (n=60)

Characteristic	Number (n)	Percentage (%)
Sex		
Male	24	40
Female	36	60
Diabetes mellitus		
No	42	70
Yes	18	30
Hypertension		
No	26	43.3
Yes	34	56.7
Vascular Access		
Arterio-venous Fistula	50	83.3
Catheter	9	15
Arterio-venous Graft	1	1.7
Ischemic Heart Disease		
No	55	91.7
Yes	5	8.3
Etiology of chronic kidney disease		
Analgesics nephropathy	2	3.3
Chronic pyelonephritis	5	8.3
Diabetes mellitus	18	30
Genetic	4	5
Glomerulonephritis	6	10
Hypertension	14	23.4
Nephrolithiasis	6	10
Systemic lupus erythematosus	3	4.5

Unknown	2	3.3
Total	60	100
Population categorization based on echocardiographic findings		
Ejection Fraction		
Normal	49	81.6
Mild impairment	7	11.7
Moderate impairment	4	6.7
Total	60	100
Estimated pulmonary artery pressure		
Normal	39	65
High	21	35

Table 2: Demographic and clinical characteristics of subgroups

Characteristics	**Group A** (PH absent) **(n = 39)**	**Group B** (PH present) **(n = 21)**	***P***
Gender			
Female (n)	22 (56.4%)	14 (66.7%)	0.439
Male (n)	17 (43.6%)	7 (33.3%)	
Age (years)	47.75 ± 10.08	43.31 ± 11.68	0.277
Interdialytic weight gain (kg)	1.92 ± 0.97	2.88 ± 1.10	0.010
Body Mass Index (kg/sq.m)	28.16 ± 3.48	26.84 ± 3.33	0.063
Hemoglobin (g/dL)	10.94 ± 2.22	9.37 ± 2.10	0.066
Cholesterol (mg/dL)	199.44 ± 38.36	203.88 ± 41.48	0.786
Albumin (g/dL)	3.69 ± 0.71	3.66 ± 0.57	0.713
Calcium (mg/dL)	9.39 ± 0.81	9.48 ± 0.83	0.716
Phosphate(mg/dL)	4.46 ± 1.27	4.41 ± 1.06	0.806
Blood Urea Nitrogen (mg/dl)	67.13 ± 23.50	64.38 ± 8.4	0.452

* All measurements are expressed as mean ± SD or Number (percent) as indicated

Table 3: Echocardiographic parameters of population subgroups

Characteristics	**Group A** (PH absent) **(n = 39)**	**Group B** (PH present) **(n = 21)**	***P***
LVEDV (mm)	5.08 ± 0.79	5.44 ± 0.56	0.015
LVESV (mm)	3.37± 0.81	3.92 ± 0.72	0.001
EF (%)	62.47 ± 7.49	54.75 ± 10.46	0.003
FS (%)	32.53 ± 4.79	27.38 ± 6.31	0.001
LA (mm)	3.43 ± 0.59	3.75 ± 0.82	0.018
AR (mm)	3.13 ± 0.52	3.29 ± 0.34	0.257
SPAP (mm Hg)	28.94 ± 6.04	47.81 ± 8.56	0.000
Systolic dysfunction			
Normal	36 (92.3%)	13 (61.9%)	0.015
Mild	2 (5.1%)	5 (23.8%)	
Moderate	1 (2.6%)	3 (14.3%)	
Severe	-	-	
Diastolic dysfunction			
Normal	22 (59.0%)	10 (47.6%)	0.606
I	13 (33.7%)	8 (38.1%)	
II	3 (7.3%)	3 (14.3%)	
III	-	-	

* All measurements are expressed as mean ± SD or Number (percent) as indicated

Abbreviations: LVEDV Left Ventricular End Diastolic Volume; LVESV Left Ventricular End systolic Volume; EF Ejection fraction; FS Fractional shortening; LA Left atrium; AR Aortic root; SPAP Systolic pulmonary artery pressure.

Table 4: Correlation between SPAP and other variables

Variable	**Pearson's correlation coefficient (r)**	***P***
Age (years)	-0.066	0.618
BMI (kg/sq.m)	-0.119	0.365
Interdialytic weight gain (kg)	0.348	0.007
Hb (g/L)	0.249	0.055
Cholesterol (mg/dL)	0.109	0.407
Albumin (g/L)	-0.075	0.569
Calcium (mg/dL)	0.010	0.942
Phosphate (mg/dL)	0.016	0.906
BUN (mg/dL)	0.122	0.352
Creatinine (mg/dL)	-0.099	0.450
LVEDV (mm)	0.404	0.001
LVESV (mm)	0.440	0.000
LA (mm)	0.333	0.009
AR (mm)	0.173	0.229
EF (%)	-0.413	0.001
FS (%)	-0.380	0.004

Abbreviations: BMI Body Mass Index; Hb Hemoglobin; BUN Blood Urea Nitrogen; LVEDV Left Ventricular End Diastolic Volume; LVESV Left Ventricular End Systolic Volume; LA Left Atrium; AR Aortic Root; EF Ejection Fraction. FS Fractional Shortening.

Table 5: Linear Regression Analysis

ANOVA[a]

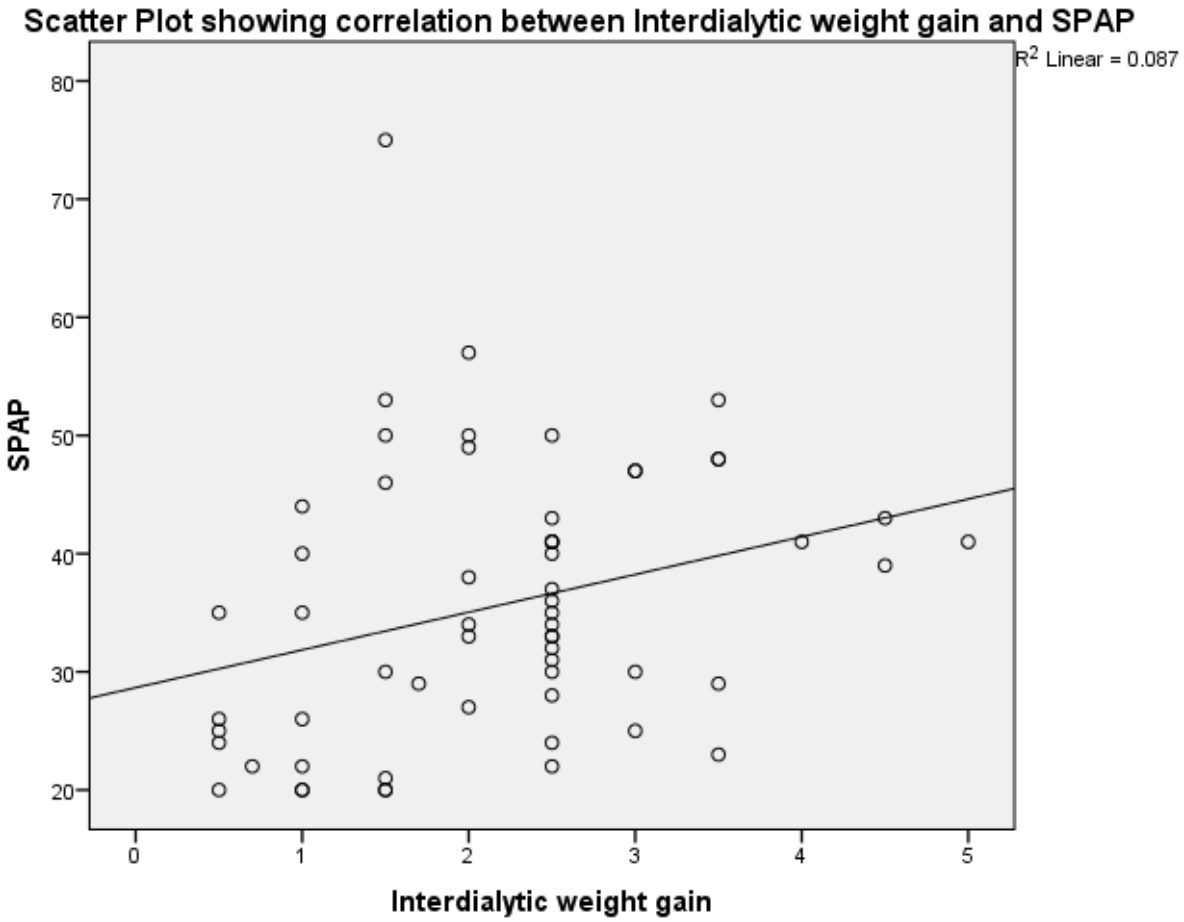
Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	666.861	1	666.861	5.521	.022[b]
	Residual	7005.539	58	120.785		
	Total	7672.400	59			

a. Dependent Variable: SPAP
b. Predictors: (Constant), Interdialytic wt gain

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	Constant	28.664	3.275		8.752	.000	22.108	35.220
	wtgain	3.191	1.358	.295	2.350	.022	.473	5.910

a. Dependent Variable: SPAP

Figure 3: Correlation of SPAP with Interdialytic weight gain



Discussion

The prevalence of PH matches with previous studies by Canan *et al*. (21.6%), Tarrass *et al*. (26.74%) and Amin *et al.* (29%) on HD patients via arteriovenous access [21-23]. Abdelwhab and Elshinnawy have observed PH in 20/45 (44.4%) of ESRD patients on regular HD and in 10/31 (32.3%) of CKD patients on conservative treatment [24]. A higher prevalence of PH has been reported by Nakhoul *et al.* (48%), Yigla *et al.* (39.7%), and Mazdeh *et al.* (51.6%) in ESRD patients on regular HD [7, 11, 25]. The higher prevalence may be attributed to many factors [28]. Firstly, a different methodology was used in these studies, as they performed Doppler echocardiogram on the day after dialysis, which may have led to a higher fluid volume load. Secondly, some of these studies may not have strictly excluded patients with co-morbid conditions such as, associated illnesses and smoking. Thirdly, varying definitions of PH will also account for varying prevalence estimates. For example, in a study from the USA, using a SPAP ≥ 35 mm Hg yielded a prevalence of 47%, while it reduced to only 20% when PH was defined by SPAP ≥ 45 mm Hg [12]. This is similar to the 16% prevalence estimate seen in the study by Agarwal *et al.* when PH was defined as SPAP ≥ 45 mm Hg [14]. Fourthly, variable degrees of chronic volume overload may also confound the prevalence. It is difficult to account for this variable among studies, as there are no established markers of chronic volume overload.

Determinants of pulmonary hypertension

There are multiple determinants of PH that have been suggested by other authors. Some of the major ones have been noted to be the following: increased age [12], female gender [23], lower body mass index [12], high CO [7,11], low hemoglobin [11], reduced nitric oxide metabolites [7], dialysis duration [27], low diastolic BP [27] and left ventricular diastolic dysfunction [24]. In the present study however, PH was associated with higher LVEDV,

LVESV, LA and AR diameters. Along with increased heart dimensions, PH was also associated with systolic dysfunction; indicated by reduced ejection fraction; but no significant diastolic dysfunction was observed. In contrast to Mousavi et al. study [18], but in agreement with Agarwal et al. [14] and Fadaii et al. [32], lower ejection fraction was found to be linked to the high prevalence of PH in the present study. This may reflect chronic fluid volume overload or poor myocardial performance. However, poor systolic myocardial performance per se is unlikely to be a reason because those with PH had a statistically significant correlation with interdialytic weight gain. That was further evaluated with a regression analysis to investigate whether interdialytic weight gain can be regarded a predictor of PH in HD population.

In the current study, comparison of the clinical and metabolic variables of two groups revealed that the patients with PH (Group B) had an observed lower hemoglobin and albumin levels, as well as higher cholesterol level than the normal pulmonary pressure group, albeit statistically non-significant. Shoukat et al. found lower hemoglobin and albumin levels, and Floege and Ketteler did not find a difference in the lipid profile of patients with PH, compared to normal patients [29,30].

The present study was limited to determine the frequency, and some of the major factors affecting PH. Other factors like recurrent air embolism need to be studied for their influence on PH. The number of patients was relatively small in comparison with other similar studies, possibly due to the stringent exclusion criteria used in the current study, as a majority of ESRD patients had concomitant cardiac or pulmonary disease. Also, the secondary causes of PH have not been studied. Another possible limitation could be the use of non-invasive Doppler echocardiographic measurement of SPAP. However, echocardiographic measurements are reported to have an excellent correlation with direct invasive measurements. There is a need to study the outcome of those who developed PH in relation to those who did not develop the PH and their survival. Further, basic and clinical research is needed to understand the pathogenic factors as well as sophisticated therapeutic options that may improve the morbidity, mortality and quality-of-life parameters in dialysis patients with PH.

Conclusions

There are a substantial number of ESRD patients on maintenance HD who have functional abnormality of pulmonary circulation. Such patients develop an unusual outline of PH associated with high interdialytic weight gain along with probable AVF mediated increased CO and pulmonary vasoconstriction as well as pulmonary endothelial dysfunction, due to the deranged balance between vasoconstrictive and vasodilatory mechanisms, increased vasoproliferation, systemic and local inflammation and renal anemia.

The issue of PH in dialysis patients is clinically important, under-recognized and can lead to increased morbidity and mortality in this group of patients. It is recommended that patients scheduled for HD be screened for PH before the initiation of dialysis. Estimation and follow up of SPAP using echocardiography may be indicated in all patients on HD. Increased unexplained PAP is a call for further investigation to rule out possible secondary causes of PH.

PH may be associated with mild to moderate impairment of cardiac systolic function. That seems to be related to chronic fluid volume overload and increased interdialytic weight gain. Careful assessment of volume state along with encouraging patients to limit interdialytic weight gain may help reduce SPAP.

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