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Study of Pulmonary Hypertension in Hemodialysis patients in Sohag University Hospital

Lofty H. Abo-Dahab, Ahmed M. Boghdady, Nayel A. Zaki, Noher Mohammad Abass

Department of Internal Medicine, Sohag Faculty of Medicine, Sohag University

Introduction

Chronic kidney disease (CKD) is a global health burden with a high economic cost to health systems and is an independent risk factor for cardiovascular disease (CVD)[1]**.** Pulmonary hypertension (PHT) is a common co-morbidity in patients with CKD and end-stage renal disease (ESRD) [2]**.** PH is associated with increased risk of hospitalization and mortality in patients with CKD [3]**.**Several studies demonstrated that PH is an independent predictor of mortality in patients with CKD, especially those receiving renal replacement therapy (RRT)[4] **.**Coexisting left side heart disease, chronic lung disease, thromboembolic disease, autoimmune diseases and liver disease that are well-established risk factors for developing PH may occur in patients with CKD. However, CKD especially ESRD by itself proposed to cause pulmonary vascular remodeling and PH. Possible mechanisms that have been suggested include endothelial dysfunction due to(increased oxidative stress from uremic toxins, chronic inflammation resulting from exposure of the blood to dialysis membrane), vascular calcification, and increased flow from arteriovenous fistula (AVF) [5] **.**

Early diagnosis and early treatment of PH might improve the long-term outcomes. Therefore, it is crucial to investigate the epidemiology of PH before patients with CKD progress to ESRD [6]**.**

Patients and Methods

A cross sectional study was conducted on 124 patients with CKD who were maintained on long term regular hemodialysis therapy three times per week in 4-h sessions in hemodialysis unit in Sohag University Hospital. Ethics committee approval and informed consent were obtained **.**

Exclusion criteria

Age less than 18 years, Pulmonary diseases (chronic obstructive lung disease, chest wall or parenchymal lung disease), Congenital heart diseases, Smokers, Collagen vascular disease, Rheumatic heart disease, pregnancy and Malignancy.

Methods

A detailed clinical history and examination to all patients

Laboratory assessment

Complete blood count, Blood urea nitrogen, Serum creatinine, Liver function test, Lipogram, Serum uric acid, Serum bicarbonate, Serum calcium, phosphorus, Parathyroid hormone level.

Transthoracic Doppler echocardiography

Every patient underwent a complete two-dimensional and doppler echocardiography study (Trans-thorathic Echo (TTE): "Toshiba, NEMIO30"). TTE was done on the day post dialysis within 4h after completion of dialysis when the patients reach the "dry weight" prescribed by nephrologists on the clinical examination including BP and weight in order to avoid over estimation of PAP due to volume overload to assess:

1-Dimensions .

2-Left ventricular function.

3-Valvular lesions and its degree.

4-Estimate pulmonary artery pressure

Tricuspid regurgitation velocity (TRV) was used to determine RV systolic pressure, which is considered equal to systolic pulmonary arterial pressure (SPAP) in the absence of pulmonary outflow tract obstruction and/or pulmonic valve stenosis. This is done by calculating the systolic trans-tricuspid gradient using the modified Bernoulli equation and then adding calculated right atrial pressure (RAP) which estimated from IVC and its collapsibility[7] **.**

Statistical analysis

Statistical package for social sciences (IBM-SPSS), version 24 IBM-Chicago, USA (May 2016) was used for statistical data analysis. Data expressed as mean, standard deviation (SD), number and percentage. Mean and standard deviation were used as descriptive value for quantitative data, while number and percentage were used to describe qualitative data.

§ **Chi-Square test** was used for comparison between qualitative variables. Quantitative data was tested for normality by **Shapiro–Wilk test.**

Results of the study

Data on the 61(out of 124) patients with PH were compared with the 63 patients without PH in the hemodialysis patients. Diabetes mellitus and hypertension were the most common etiologies of renal failure in both subgroups. Brachial AVF; 43 out of 61 patients (70.5%) represent the majority of patients in PH subgroup, and radial AVF; 43 out of 63 (68.3%) represent the majority of patients in normal PAP subgroup of hemodialysis patients. There was a highly statistically significant increase in age, duration of dialysis treatment, serum phosphorous, serum parathyroid hormone and highly statistically significant decrease in serum calcium, HB level, Hematocrit % in PH subgroup compared to normal PAP subgroup. There is no statistically significant difference between both subgroups regarding ejection fraction. There is a highly statistically significant difference between both subgroups regarding RVH which demonstrated among 45 patients (73.8%) in PH subgroup comparing to 14 patients (22.2%) without PH subgroup . LVH which demonstrated among 40 patients (65.6%) in PH subgroup comparing to 21 patients (33.3%) without PH subgroup, left atrial diameter, LVEDD, LVESD were higher in patients with PH subgroup comparing patients without PH subgroup. Valvular calcification was demonstrated among 21 patients (34.4%) in PH subgroup comparing to 3 patients (4.8%) without PH subgroup with Statistically significant difference (p-value< 0.001). Diastolic dysfunction was demonstrated among 40 patients (65.6%) with PH subgroup comparing to 19 patients (30.2%) without PH subgroup with highly statistically difference between both subgroups.(p-value < 0.001) .

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Table (1): Comparison between hemodialysis patients (with or without pulmonary hypertension) regarding clinical data:

Parameter	Hemodialysis patients		P-value
	Without PH (N= 63)	With PH (N= 61)	
Age (year) • Mean± S.D. • Median (Range)	38.9 ± 10.4 40 (19 – 62)	48 ± 10.8 45 (30 – 77)	<0.001
Sex • Males (%) • Females (%)	44 (69.8%) 19 (30.2%)	41 (67.2%) 20 (32.8%)	0.753
Body mass index	28.8 ± 6.2	26.4 ± 4.9	> 0.05
Duration of hemodialysis (year) • Mean± S.D. • Median (Range)	4.4 ± 1.7 5 (1 – 11)	8.5 ± 2.3 8 (1 – 16)	< 0.001
Access location • Brachial (%) • Radial (%)	20 (31.7%) 43 (68.3%)	43 (70.5%) 18 (29.5%)	< 0.001

Table (2): Comparison between patients on hemodialysis (with or without pulmonary hypertension) regarding HB level, HCT:

Parameter	Hemodialysis patients		P-value
	Without PH (N= 63)	With PH (N= 61)	
HB (g/dl) • Mean± S.D. • Median (Rang)	10.4 ± 0.9 10.5 (7.9 – 13.8)	8.4 ± 1.2 8.5 (5.6 – 12)	< 0.001
HCT (%) • Mean± S.D. • Median(Range)	30.8 ± 2.09 30 (26 – 41)	29.8 ± 3.9 29 (20.1 – 47)	< 0.002

Table (3): Comparison between patients on hemodialysis (with or without pulmonary hypertension) regarding PTH level, serum calcium, serum phosphorus**:**

Parameter	Hemodialysis patients		P-value
	Without PH (N= 63)	With PH (N= 61)	
PTH level (pg/ml) • Mean± S.D. • Median (Range)	325.1 ± 362.9 210 (65 – 1675)	895.1 ± 527.4 962 (75 – 1900)	< 0.001
Serum Calcium (mg/dl) • Mean± S.D. • Median (Range)	9.6 ± 1.4 9.1 (7.9 – 15.3)	8.9 ± 0.9 8.8 (6.6 – 12)	< 0.001
Serum Po4 (mg/dl) • Mean± S.D. • Median (Range)	3.7 ± 0.6 3.6 (0.8 – 5)	4.4 ± 0.7 4.2 (3.5 – 8.1)	< 0.001

Table (4): Comparison of hemodialysis patients (with or without pulmonary hypertension) regarding Echocardiography findings:

Parameter	Hemodialysis patients		P-value
	Without PH (N= 63)	With PH (N= 61)	
Right side:			
Right ventricular hypertrophy:			< 0.001
• No (%)	49 (77.8%)	16 (26.2%)	
• Yes (%)	14 (22.2%)	45 (73.8%)	
Left ventricle:			
left ventricular hypertrophy			< 0.001
• No (%)	42 (66.7%)	21 (34.4%)	
• Yes (%)	21 (33.3%)	40 (65.6%)	
LVEDd (cm)			0.048
• Mean± S.D.	4.6 ± 0.8	4.9 ± 1.01	
• Median (Range)	4.6 (3.3 – 6.9)	5 (2.75 – 6.7)	
LVESd (cm)			< 0.001
• Mean± S.D.	3.1 ± 0.7	3.6 ± 0.6	
• Median (Range)	3 (2 – 5.3)	3.5 (2.1 – 6)	
Ejection fraction (%)			0.685
• Mean± S.D.	58.4 ± 4.2	57.7 ± 6.3	
• Median (Range)	60 (47 – 66)	60 (33 – 67)	
Diastolic dysfunction			< 0.001
• No (%)	44 (69.8%)	21 (34.4%)	
• Yes (%)	19 (30.2%)	40 (65.6%)	
Left atrium:			
Left atrium diameter (cm)			0.002
• Mean± S.D.	3.4 ± 0.5	3.8 ± 0.7	
• Median (Range)	3.4 (2.3 – 4.5)	3.7 (2.5 – 5.4)	
Others:			
Valvular calcification			< 0.001
• No (%)	60 (95.2%)	40 (65.6%)	
• Yes (%)	3 (4.8%)	21 (34.4%)	

Discussion

The current study reported that PH (SPAP> 35 mmHg) was demonstrated in(49%) among 124 patients receiving long-term hemodialysis with a mean systolic PAP of (43.1± 7.2 mmHg). This is in concordance with **Yigla et al., (2003)** who reported that the prevalence of PH was 39.7% in HD patients with a mean (44± 7 mmHg). In addition, **Mahdavi-Mazdeh et al., (2008)** reported that the prevalence of PH ranges from 30–40% as detected by Doppler echocardiography in HD patients. Also, **Abdelwhab et al., (2008)** demonstrated that PH was found in 44.4% in HD patients The higher prevalence of PH in CKD could be explained by multiple factors, where the main determinants of pulmonary arterial pressure are cardiac output, pulmonary vascular resistance and pulmonary capillary wedge pressure, all these factors can be altered at a variable extent in CKD patients (**Sise et al., 2013).** Thus, an increase in cardiac output due to hyperdynamic circulation secondary to AVF, anemia and volume overload affects some of the CKD patients (**Stauffer et al., 2014) (Tsai et al., 2014).** This study show a highly statistically significant increase in age in PH subgroup in hemodialysis group. Similar to **Magdy et al ., (2013)** who found a highly statistically significant increase in age, a positive significant correlation between PAP and age. The present study found no significant difference between gender and development of PH. Similarly, **Tarrass et al., (2006)** and **Kumbar et al., (2007)** reported that there was no

difference between gender and development of PH. In the present study there was a highly statistically significant increase in duration of dialysis treatment in PH subgroup in hemodialysis group. Similar findings was demonstrated by **Jawad, (2009)** who found that the presence of PH was related to long duration of hemodialysis. In addition, **Abdallah et al., (2010)** demonstrated that CKD duration and AV fistula duration were positively correlated with systolic PAP in patients receiving hemodialysis. In contrast, **Amin et al., (2003)** and **Tarrass et al., (2006)** reported that there was no significant difference between patients with PH and those without PH as regards to duration of dialysis. In this study there are 43 out of 61 patients (70.5%) with brachial AVF location had PH, in contrast to 18 patients (29.5%) with radial AVF location had PH among hemodialysis patients, which was a highly statistically significant difference ($p < 0.001$) .Also, **Magdy et al ., (2013)** reported that Brachial AVF; 23 out of 27 patients (85.18%) represent the majority of patients in the PH subgroup, and radial AVF; 23 out of 38 (60.52%) represent the majority of patients in the normal PAP subgroup of HD patients in his study . Fistula that is created in a large vessel has higher AVF blood flow, higher COP, increased sympathetic activity resulting in an increase in myocardial contractility and heart rate, increased pulmonary blood flow. On the other hand, **Tarrass et al., (2006)** demonstrated that, the effect of AVF location was not statistically significant**.** The current study demonstrated a highly statistically significant decrease in hemoglobin level, haematocrite level in PH subgroup in HD group . Similarly, **Yigla et al., (2003)** compared data on 23 patients with PH receiving HD with 35 patients without PH receiving HD and reported that the hemoglobin and hematocrit levels were significantly lower in the PH subgroup. Also, **Buemi et al., (2007)** reported that the association between lower hemoglobin levels and PH may be explained by tissue hypoxia triggered by lower hemoglobin levels may increase PAP in CKD. The current study demonstrated a highly statistically significant increase in parathyroid hormone level in PH subgroup in HD group as well as conservative group.

Similarly, **Mousavi et al., (2014)** reported that a significant increase in parathyroid hormone level in PH compared with normal pulmonary artery pressure in HD patients. Also, **Demir et al., (2013)** stated that hyperparathyroidism as a consequence of low vitamin D levels was related with higher pulmonary artery pressure.

In the other hand, **Amin et al., (2003**) reported that there was no significant difference between patients with PH and those without PH in HD patients regarding PTH level [420± 512 pg/mL vs 354 ± 519 pg/mL]. The current study demonstrated a highly statistically significant increase in serum phosphorus level in PH subgroup in HD .Similarly, **Magdy et al., (2013)** reported that there is a positive significant correlation between PAP and serum phosphorous. In the other hand, **Amin et al., (2003)** reported that there was no significant difference between patients with PH and those without PH in HD regarding to serum phosphorus The current study demonstrated that a highly statistically significant decrease in serum calcium in PH subgroup in HD patients. Similarly, **Kumbar et al., (2007**) reported that the serum calcium level was significantly lower in the patients with PH. In the other hand, **Amin et al., (2003**) reported that there

was no significant difference between patients with PH and those without PH in HD regarding serum calcium (9.6 ±2 mg/dL vs 10 ± 2 mg/dL). The current study reported a highly statistically significant increase in LVH in PH subgroup in HD. LVH is the most frequently observed cardiac abnormality in CKD patients (**Park et al., 2012)**. LVH is significantly associated with CVD events and mortality **(Paoletti et al., 2004)**. The current study reported no statistically significant difference in systolic function in PH subgroup in HD. The current study demonstrated a highly statistically significant increase in left atrial diameter in PH subgroup in HD. The present study demonstrated a highly statistically significant increase in diastolic dysfunction in PH subgroup in HD. There is a highly statistically significant difference in valvular calcification which was higher in PH subgroup in HD.

Limitation of the study

- We have only estimated the PASP by echocardiography, instead of measuring it directly by RHC. Because of its invasive nature, Most of studies use the estimate PASP by transthoracic echocardiography because of its noninvasive nature and the good correlation with RHC.
- No information about volume status or body composition analysis by bio impedance was collected.

Conclusion

§ PH is a common finding in CKD patients; the prevalence was highest among patients with ESRD receiving long-term hemodialysis than those on conservative management.

§ Early detection of PH is important in order to avoid the serious consequences of the disease.

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