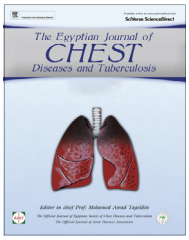
Egyptian Journal of Chest Diseases and Tuberculosis (2013) **62**, 761–768

The Egyptian Society of Chest Diseases and Tuberculosis

Egyptian Journal of Chest Diseases and Tuberculosis

www.elsevier.com/locate/ejcdt
www.sciencedirect.com



ORIGINAL ARTICLE

Prevalence of pulmonary hypertension in patients with chronic kidney disease on and without dialysis

Magdy M. Emara [a,g,*], Mohamad A. Habeb [b], Alsayed Ahmed Alnahal [c], Tarek A. Elshazly [d], Faisal O. Alatawi [e], Amer S. Masoud [f]

[a] *Department of Thoracic Medicine, Mansoura University, Egypt*
[b] *Department of Thoracic Medicine, Zagazig University, Egypt*
[c] *Department of Internal Medicine (Nephrology), Zagazig University, Egypt*
[d] *Department of Internal Medicine, Mansoura University, Egypt*
[e] *Department of Internal Medicine (Cardiology), Taibaha University, Al-Madinah AL-Munawarah, Saudi Arabia*
[f] *Department of Public Health & Community Medicine, AlAzhar University, Egypt*
[g] *Department of Internal Medicine (Pulmonology), College of Medicine, Taibah University, AL-Madinah AL-Munawarah, Saudi Arabia*

Received 9 January 2013; accepted 4 September 2013
Available online 8 October 2013

KEYWORDS

Pulmonary hypertension;
Chronic kidney disease;
Dialysis

Abstract *Background:* Pulmonary arterial hypertension is a newly recognized disease in patients with renal disease. In a recent review, the prevalence of PHT in ESRD patients was reported to be around 40–50%.

Aim of the work: To evaluate the prevalence of primary pulmonary hypertension among CKD patients on and without dialysis and to compare clinical, hemodynamic, and metabolic variables among patients with and without PH to search for possible etiologic factors.

Patients and methods: Our study included 99 CKD patients; 65 patients on hemodialysis, 12 on peritoneal dialysis and 22 on conservative management. Detailed medical history, examination, and complete laboratory investigations were obtained. Systolic PAP, EF% and cardiac output were evaluated by Doppler echocardiography and AVF flow by Doppler ultrasound.

Abbreviations: ESRD, end stage renal disease; CKD, chronic kidney disease; PAH, pulmonary arterial hypertension

* Corresponding author. Address: Department of Thoracic Medicine, Mansoura University, Mansoura 35516, Egypt. Tel.: +20 966509824140.
E-mail address: magdyemara@live.com (M.M. Emara).

Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.

ELSEVIER Production and hosting by Elsevier

 http://dx.doi.org/10.1016/j.ejcdt.2013.09.011

Results: A high prevalence of pulmonary hypertension was demonstrated among 27 patients (41.53%) receiving long-term hemodialysis with a mean systolic PAP of 49.33 ± 9.18 mmHg; as well as in two patients (16.66%) receiving peritoneal dialysis 43 ± 1.41 mmHg, and in five patients ((22.72%) receiving conservative management 44.8 ± 5.89 mmHg.

Conclusion: This study demonstrated a high prevalence of pulmonary hypertension among patients with CKD on and without dialysis. The prevalence was highest among patients with ESRD receiving long-term hemodialysis (41.53%) especially in patients with older age, longer duration of dialysis treatment, higher AV fistula flow, cardiac output.

Introduction

Pulmonary hypertension (PHT) is a progressive disorder complicating heart, lung, or systemic diseases, with increased morbidity and mortality regardless of its etiology [1]. Pulmonary arterial hypertension (PAH) is a newly recognized disease in patients with renal disease [2]. In a recent review, the prevalence of PHT in ESRD patients was reported to be around 40–50% [3]. Pulmonary hypertension, defined as systolic pulmonary artery pressure (SPAP) > 35 mmHg at rest as estimated by Doppler echocardiography, has been repeatedly reported in patients with chronic kidney disease, both predialysis and during regular renal replacement therapy, with a high but variable prevalence [4,5]. Its presence has been recently suggested to be associated with a worse outcome [6]. A number of causative factors have been related to this pathological finding: pulmonary artery calcifications secondary to hyperparathyroidism [5]; and hemodynamic modifications related to the creation of an arteriovenous fistula (AVF), caused by a reduced ability of pulmonary vessels to accommodate the AV access-mediated elevated cardiac output, possibly because of a derangement of nitric oxide–endothelin metabolism [6] but its pathogenesis has not been completely elucidated.

Patients and methods

Our-cross-sectional and retrospective study included a total of 99 CKD patients who were followed up at nephrology center of King Fahd hospital, Al-Madinah Al-Munawarah, the Kingdom of Saudi Arabia at the period between January 2010 and December 2011. They were divided into three groups; group I involved 65 patients (34males, and 31 females with a mean age 45.72 ± 7.83 years) who were maintained on long-term regular hemodialysis therapy via arteriovenous fistulas (38 radial and 27 brachial AVF) three times per week in 4-h sessions, group II included 12 patients (7 males, and 5 females with a mean age 46.08 ± 3.84 years) on continuous ambulatory peritoneal dialysis and group III included 22 patients (13 males, and 9 females with a mean age 45.45 ± 3.77 years) on conservative management. Diabetic nephropathy was the commonest cause of uremia ($n = 40$), then hypertensive nephropathy ($n = 31$), Glomerulonephritis ($n = 16$), chronic pyelonephritis ($n = 6$), cystic renal disease ($n = 4$), whereas two patients had undetermined renal diagnosis. All patients included in this study underwent the following:

(1) A detailed clinical examination including age; sex; smoking habits; associated comorbidity particularly diabetes mellitus and hypertension; age at time of CKD, etiology of renal failure, duration of dialysis treatment, and access location of AVF [brachial or radial].
(2) Laboratory investigation included levels of hemoglobin, hematocrit, blood urea nitrogen, serum creatinine, serum bicarbonate, serum calcium, phosphorus, parathyroid hormone level. Average levels measured at least twice in the study period were calculated.
(3) Transthoracic Doppler echocardiography: Every patient underwent a complete two-dimensional and Doppler echocardiography study on the day post dialysis within 4 h after completion of dialysis when the patient had reached the "dry weight" prescribed by nephrologists on the clinical examination including BP and weight in order to avoid overestimation of PAP due to volume overload. In PD patients there was no such specification. One experienced cardiologist performed all examinations using an Acuson Sequoia, 512 (Mountain View, CA, USA) ultrasound machine. The results of transthoracic Doppler echocardiography were used to determine the pulmonary artery pressure (PAP), left ventricular function, ejection fraction, and cardiac output.

Systolic PAP: A tricuspid regurgitation systolic jet was recorded from the parasternal or apical window with the continuous-wave Doppler echocardiography probe. Systolic right ventricular (or pulmonary artery) pressure was calculated using the modified Bernoulli equation: PAP = 4 × (tricuspid systolic jet) 2 + 10 mmHg (estimated right atrial pressure) [7]. According to Yigla et al. [6] PHT was defined as a systolic PAP > 35 mmHg. Patients with PHT > 35 mmHg were evaluated further by a pulmonologist in order to uncover other potential causes of PHT. This assessment included history, physical examination, chest radiograph, chest CT, complete pulmonary function tests, and measurement of arterial blood gases.

Cardiac output was estimated from the left ventricular outflow tract velocity time integral × diameter [8].

(1) *Doppler sonography:* AVF flow measurement in hemodialysis patients by Doppler ultrasound was done.

Exclusion criteria included

Smokers, any cardiovascular and pulmonary diseases (chronic obstructive lung disease, chest wall or parenchymal lung disease) which lead to pulmonary hypertension as well as patients

with chronic coronary heart disease, previous pulmonary embolism, collagen vascular disease, volume overload at the time of echocardiography were excluded. All patients provided written, informed consent.

Statistical analysis

The prevalence of PHT was calculated using the SPSS software. Clinical, hemodynamic, and metabolic variables were compared between patients with and without PHT with "*t*" test. Values were expressed as mean ± Standard deviation (SD) and as percentage for categorial parameters. Differences between groups were compared with Student's *t*-test for parametric continuous variables. Chi-square test was applied for estimating the occurrence of categorical variables. Pearson's correlation coefficient was used to test the relationship between PAP and other parameters. A P value < 0.05 was used as the threshold of statistical significance.

Results

The most common etiologies of renal failure were diabetes mellitus and arterial hypertension in all studied groups. Duration of dialysis treatment was highly statistically significant longer in hemodialysis than peritoneal dialysis group. Our results showed a highly statistically significant decrease in hemoglobin, hematocrit %, and statistically significant increase in creatinine, phosphorous, SPAP, and EF% in the hemodialysis group compared to the conservative management group. But no differences were found between both groups with respect to age, blood urea, serum HCO3, serum calcium, serum parathyroid hormone level or cardiac output. As regards peritoneal dialysis group, there was a highly statistically significant decrease in cardiac output, and statistically significant increase in serum calcium, phosphorous compared to the conservative management group. But, no differences were found between both groups with respect to age, hemoglobin, hematocrit %, blood urea, serum HCO3, serum parathyroid hormone level, SPAP, or EF%. A high prevalence of pulmonary hypertension (SPAP > 35 mmHg) was demonstrated among 27 patients (41.53%) receiving long-term hemodialysis; as well as in two patients (16.66%) receiving peritoneal dialysis, and in five patients (22.72%) receiving conservative management. Hemodialysis group has the highest mortality 14 out of 65 patients (21.54%), then peritoneal dialysis group two patients (16.66%) (Table 1).

Data on the 27 (out of 65) patients with pulmonary hypertension were compared with the 38 patients without pulmonary hypertension in the hemodialysis group. Diabetes mellitus and hypertension were the most common etiologies of renal failure in both subgroups in all studied patients. Brachial AVF; 23 out of 27 patients (85.18%) represent the majority of patients in pulmonary hypertension subgroup, and radial AVF; 23 out of 38 (60.52%) 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 creatinine, serum phosphorous, serum parathyroid hormone, SPAP, cardiac output, and AVF flow and highly statistically significant decrease in serum HCO3, EF% in pulmonary hypertension subgroup compared to normal PAP subgroup. But no differences were found between both subgroups with respect to hemoglobin, hematocrit %, blood urea, and serum calcium of hemodialysis patients. Mortality was higher in the pulmonary hypertension subgroup (11 out of 27 patients (40.74%). As regards peritoneal dialysis group, there was a highly statistically significant increase in age, duration of dialysis treatment, blood urea, serum creatinine, SPAP, and cardiac output in pulmonary hypertension subgroup compared to normal PAP subgroup. But no differences were found between both subgroups with respect to hemoglobin, hematocrit %, serum HCO3, serum calcium, serum phosphorous, serum parathyroid hormone, and EF%. Data on the 5 (out of 22) patients with pulmonary hypertension were compared with the 17 patients without pulmonary hypertension in the conservative management group. There were highly statistically significant increases in blood urea, serum creatinine, serum parathyroid hormone, SPAP, and cardiac output, and a highly statistically significant decrease in serum HCO3, and serum calcium in the pulmonary hypertension subgroup compared to the normal PAP subgroup. But no differences were found between both subgroups with respect to age, hemoglobin, hematocrit %, serum phosphorous, and EF% (Table 2).

On comparing data of pulmonary hypertension subgroups of peritoneal dialysis and conservative management with hemodialysis subgroup, hematocrit % was statistically significantly lower in the hemodialysis subgroup than other both subgroups. But, serum creatinine, serum phosphorous, SPAP, and cardiac output were statistically significant higher in the hemodialysis subgroup than both peritoneal dialysis and conservative management subgroups (Table 3).

Our results revealed a positive significant correlation between PAP and age, duration of dialysis treatment, blood urea, serum creatinine, serum phosphorous, serum parathyroid hormone, cardiac output, and AVF flow as well as an inverse correlation between PAP, serum HCO3 and EF% in the hemodialysis group. A positive significant correlation was found between PAP and age, duration of dialysis treatment, blood urea, and cardiac output in peritoneal dialysis group. In the conservative management group there was a positive significant correlation between PAP and blood urea, serum creatinine, serum parathyroid hormone, and cardiac output as well as an inverse correlation between PAP, serum HCO3 and serum calcium (Table 4).

Discussion

The prevalence of chronic kidney disease (CKD) in the developed world is 13% and is recognized as a condition that elevates the risk of cardiovascular complications as well as kidney failure and other complications [9]. End-stage kidney disease (ESKD) substantially increases the risk of death, cardiovascular disease, and use of specialized health care [10]. Pulmonary hypertension (PHT) has been reported to be high among end-stage renal disease (ESRD) patients [11]. In clinical practice, shunting of blood from the left to the right side of the heart and increased cardiac output and pulmonary blood flow are common medical conditions resulting in PAH [12]. However, Yigla et al. [13] first noted unexplained PAH in some long-term hemodialysis (HD) patients during an epidemiologic study [13]. Both end-stage renal disease and long-term hemodialysis via arteriovenous fistula may be involved in the

Table 1 Clinical and laboratory data of studied groups.

	Hemodialysis group (No. = 65)	Peritoneal dialysis group (No. = 12)	Conservative management group (No. = 22)
Age (years)	45.72 ± 7.83 ***P* > .05**	46.08 ± 3.84 ***P* > .05**	45.45 ± 3.77
Sex			
Male	34 (52.3%)	7 (58.33%)	13 (59%)
Female	31 (47.7%)	5 (41.67%)	9 (41%)
Etiology of RF			
DM	26 (40%)	5 (41.67%)	9 (40.9%)
HTN	19 (29.24%)	4 (33.34%)	8 (36.36%)
Glomerulonephritis	13 (10.86%)	1 (8.32%)	2 (9.1%)
Pyelonephritis	2 (9.1%)	2 (1.66%)	2 (9.1%)
Cystic renal disease	3 (4.61%)	0	1 (4.54%)
Undetermined renal diagnosis	2 (3.07%)	0	0
Access location of AVF			
Brachial	38 (58.46%)		
Radial	27 (41.53%)		
Duration of dialysis treatment (months)	80.93 ± 16.96	42.66 ± 13.70 ***P* < 0.001**	
Hemoglobin (gm/dl)	10.45 ± 1.18 ***P* < 0.001**	11.24 ± 1.30 ***P* > 0.05**	11.45 ± 1.22
Hematocrit %	29.93 ± 1.75 ***P* < 0.001**	33.08 ± 3.11 ***P* > 0.05**	34.13 ± 3.41
Blood urea nitrogen (mg/dl)	72.35 ± 12.26 ***P* > 0.05**	67.66 ± 17.32 ***P* > 0.05**	69.77 ± 17.62
S. creatinine (mg/dl)	3.97 ± 0.82 ***P* < 0.01**	3.49 ± 0.79 ***P* > 0.05**	3.48 ± 0.57
HCO3 (mEq/L)	21.13 ± 2.12 ***P* > 0.05**	21.08 ± 1.56 ***P* > 0.05**	21.36 ± 1.36
S. calcium (mg/dl)	8.84 ± 0.46 ***P* > 0.05**	9.80 ± 0.80 ***P* < 0.05**	9.12 ± 0.90
S. phosphorus (mg/dl)	4.23 ± 0.50 ***P* < 0.05**	4.52 ± 0.62 ***P* < 0.01**	3.95 ± 0.62
PTH (pg/ml)	242.38 ± 58.17 ***P* > 0.05**	233.33 ± 44.69 ***P* > 0.05**	248.50 ± 39.07
SPAP > 35 mmHg SPAP (mmHg)	27 (41.53%) 36.15 ± 13. 24 ***P* < 0.05**	2 (16.66%) 27 ± 8.49 ***P* > 0.05**	5 (22.72%) 29.72 ± 9.50
EF%	53.53 ± 7.23 ***P* < 0.05**	50.08 ± 4.39 ***P* > 0.05**	50.40 ± 4.10
Cardiac output (L/min)	5.67 ± 0.78 ***P* > 0.05**	5.10 ± 0.46 ***P* < 0.001**	5.73 ± 0.51
AVF flow (ml/min.)	463.81 ± 0.78		
Outcome			
Died	14 (21.54%)	2 (16.66%)	2 (9.09%)
Survivor	51(78.46%)	10 (83.4%)	20 (90.91%)

pathogenesis of pulmonary hypertension by affecting pulmonary vascular resistance and cardiac output. Hormonal and metabolic derangement associated with end-stage renal disease might lead to pulmonary arterial vasoconstriction and an increase in pulmonary vascular resistance. Pulmonary arterial pressure may be further increased by high cardiac output resulting from the arteriole-venous access itself, worsened by commonly occurring anemia and fluid overload [14]. On the other hand, the prevalence of PAH in patients on peritoneal dialysis (PD) is still a matter of debate [15,16]. Therefore, the aim of this study was to evaluate the prevalence of primary pulmonary hypertension (PHT) among chronic kidney disease patients on and without dialysis and to compare clinical, hemodynamic, and metabolic variables among patients with and without PH to search for possible etiologic factors. Our study demonstrated a high prevalence of pulmonary hypertension (SPAP > 35 mmHg) among 27 patients (41.53%) receiving long-term hemodialysis with a mean systolic PAP of 49.33 ± 9.18 mmHg; as well as in two patients (16.66%) receiving peritoneal dialysis with a mean systolic PAP of 43 ± 1.41 mmHg, and in five patients (22.72%) receiving conservative management with a mean systolic PAP of 44.8 ± 5.89 mmHg. This is in accordance with Domenici et al., 2010 [17] who reported that Pulmonary hypertension was found in 23/39 (58.9%) of the HD patients and 2/9 (22.2%) of the PD patients; PAP was significantly higher in HD patients than in PD patients ($P < 0.01$). Also, Patel et al. [18] demonstrated that forty-one patients had pulmonary hypertension, of whom 33% were on hemodialysis. Also, Yigla et al. [19] reported that PH > 35 mmHg was found in 39.7% of patients receiving hemodialysis (mean ± SD, 44 ± 7 mmHg; range, 37 to 65 mmHg), in none of the patients receiving PD, and in 1 of 12 predialysis patients. Similarly, Fabbian et al. [20] demonstrated that PHT (PAP > 35 mmHg) was detected in 22 patients (39%; PAP 42 ± 6 mmHg) and was diagnosed in 18.5% of PD patients and 58.6% of HD patients ($P = 0.021$). Also, Mahdavi-Mazdeh et al. [21] reported that prevalence of PHT ranges from 30–40% as detected by Doppler echocardiography in patients on chronic hemodialysis (HD) therapy. Abdelwhab and Elshinnawy [11] demonstrated that PHT was found in 44.4% in group 1 (HD) and in 32.3% in group 2 (conservative treatment). The most common etiologies of renal failure were diabetes mellitus and arterial hypertension in all groups and subgroups of our studied patients. This is similar to the results of the study conducted by Mahdavi-Mazdeh et al. [21] who reported that most common etiologies of renal failure in his studied patients were diabetes mellitus and arterial hypertension. The present study showed a highly statistically significant increase in age, duration of dialysis treatment, serum creatinine, serum phosphorous,

Table 2 Clinical and laboratory data of studied groups with and without pulmonary hypertension.

	Hemodialysis group (No. = 65)		Peritoneal dialysis group (No. = 12)		Conservative management Group (No. = 22)		Test of significance
	Normal PAP (No = 38)	Pulmonary hypertension (No = 27)	Normal PAP (No = 10)	Pulmonary hypertension (No = 2)	Normal PAP (No = 17)	Pulmonary hypertension (No = 5)	
Age (years)	42.73 ± 8.25	49.92 ± 4.77 ***P* < 0.001**	45 ± 3.19	51.5 ± 0.70 ***P* < 0.001**	44.70 ± 3.34	48 ± 4.41 ***P* > 0.05**	*T* test
Sex							
Male	23(60.52)	11(40.74%)	7(58.33%)	0	12(54.54%)	1(4.54%)	
Female	15(39.47%)	16(59.25%)	3 (25%)	2 (16.66%)	5 (22.72%)	4 (18.18%)	
Etiology of RF							
DM	16(42.10%)	10(37.03%)	4 (40%)	1(50%)	7(41.17%)	2(40%)	
HTN	11(28.94%)	9(33.33%)	3 (30%)	1(50%)	6(35.29)	1(20%)	
Glomerulo nephritis	7(18.42%)	6(17.6%)	1(10%)	0	1(5.88%)	1(20%)	
Pyelonephritis	2(5.26%)	0	2(20%)	0	1(5.88%)	1(20%)0	
Cystic renal disease	2(5.26%)	0	0	0	2(11.76%)	0	
Undetermined renal diagnosis	0	2(7.40%)	0	0	0		
Access location of AVF							
Brachial	15(39.47%)	23(85.18%)					
Radial	23(60.52%)	4(14.81%)					
Duration of dialysis treatment (months)	72.44 ± 14.31	94 ± 10.54 ***P* < 0.001**	11.6 ± 2.59	25 ± 1.41 ***P* < 0.001**			T test
Hemoglobin gm/dl	10.54 ± 1.29	10.31 ± 1.01 ***P* > 0.05**	11.39 ± 1.36	10.50 ± 0.70 ***P* > 0.05**	11.64 ± 1.32	10.80 ± 0.44 ***P* > 0.05**	T test
Hematocrit %	30.10 ± 1.79	29.70 ± 1.70 ***P* > 0.05**	32.50 ± 3.10	36 ± 0 ***P* > 0.05**	34.35 ± 3.58	33.4 ± 2.96 ***P* > 0.05**	T test
Blood urea (mg/dl)	69.92 ± 10.32	75.77 ± 14.05 ***P* > 0.05**	62.10 ± 10.77	98.50 ± 3.53 ***P* < 0.001**	63.29 ± 12.50	91.8 ± 14.8 ***P* < 0.001**	T test
S. creatinine (mg/dl)	3.60 ± 0.65	4.49 ± 0.77 ***P* < 0.001**	3.23 ± 0.55	4.77 ± 0.38 ***P* < 0.004**	3.31 ± 0.54	4.02±.25 ***P* < 0.01**	T test
HCO3 (mEq/L)	22 ± 1.88	19.92 ± 1.85 ***P* < 0.001**	21.40 ± 1.50	19.50 ± 0.70 ***P* > 0.05**	21.88 ± 1.05	19.6 ± 0.54 ***P* < 0.001**	T test
S. calcium (mg/dl)	8.81 ± 0.54	8.89 ± 0.31 ***P* > 0.05**	9.91 ± 0.84	9.25 ± 0.07 ***P* > 0.05**	9.34 ± 0.91	8.4 ± 0.35 ***P* < 0.05**	T test
S. phosphorus (mg/dl)	3.93 ± 0.26	4.64 ± 0.46 ***P* < 0.001**	4.50 ± 0.65	4.65 ± 0.63 ***P* > 0.05**	4.05 ± 0.64	3.62 ± 0.43 ***P* > 0.05**	T test
PTH (pg/ml)	207.86 ± 41.78	290.96 ± 40.66 ***P* < 0.001**	231.10 ± 46.46	244.50 ± 47.37 ***P* > 0.05**	236.7 ± 35.72	288.6 ± 17.66 ***P* < 0.006**	T test
SPAP (mmHg)	26.78 ± 5.22	49.33 ± 9.18 ***P* < 0.001**	23.80 ± 4.44	43 ± 1.41 ***P* < 0.001**	25.29 ± 4.25	44.8 ± 5.89 ***P* < 0.001**	T test
EF%	56.78 ± 5.83	48.96 ± 6.57 ***P* < 0.001**	49.80 ± 4.80	51.50 ± 0.70 ***P* > 0.05**	49.94 ± 4.08	52 ± 4.18 ***P* > 0.05**	T test
Cardiac output (L/min)	5.14 ± 0.37	6.40 ± 0.58 ***P* < 0.001**	4.93 ± 0.26	5.95 ± 0.07 ***P* < 0.001**	5.55 ± 0.43	6.34 ± 0.16 ***P* < 0.001**	T test
AVF flow (ml/min.)	409.02 ± 74	540.92 ± 58.04 ***P* < 0.001**					T test
Outcome							
Died	3(7.98%)	11(40.74%)	1(10%)	1(50%)	1(5.88%)	1(20%)	Chi-square
Survivor	35(92.10%)	16(59.25%) $\chi 2 = 8.693^{b}$ ***P* = 0.003**	9(90%)	1(50%) $\chi 2 = 1.920^{a}$ ***P* = 0.166 NS**	16(72.72%)	4(80%) $\chi 2 = 0.647^{b}$ ***P* = 0.421 NS**	

Table 3 Clinical and laboratory data of pulmonary hypertension subgroups in all studied patients.

	Conservative management group (No. = 5)	Peritoneal dialysis group (No. = 2)	Hemodialysis group (No. = 27)
Age	48 ± 4.41 ***P* > 0.05**	51.50 ± 0.70 ***P* > 0.05**	49.92 ± 4.77
Duration of dialysis		25 ± 1.41 ***P* < 0.001**	94 ± 10.54
Hemoglobin (gm/dl)	10.80 ± 0.44 ***P* > 0.05**	10.50 ± 0.70 ***P* > 0.05**	10.31 ± 1.01
Hematocrit (%)	33.40 ± 2.96 ***P* < 0.05**	36 ± 0 ***P* < 0.001**	29.70 ± 1.70
Blood urea (mg/dl)	91.80 ± 14.8 ***P* < 0.05**	98.50 ± 3.53 ***P* < 0.001**	75.77 ± 14.05
S. creatinine (mg/dl)	4.02 ± 0.25 ***P* < 0.05**	4.77 ± 0.38 ***P* > 0.05**	4.49 ± 0.77
HCO3 (mEq/L)	19.60 ± 0.54 ***P* > .05**	19.50 ± 0.70 ***P* > 0.05**	19.92 ± 1.85
S. calcium (mg/dl)	8.40 ± 0.35 ***P* > 0.05**	9.25 ± 0.07 ***P* > 0.05**	8.89 ± 0.31
S. phosphorus (mg/dl)	3.62 ± 0.43 ***P* < 0.001**	4.65 ± 0.63 ***P* > 0.05**	4.64 ± 0.46
PTH (pg/ml)	288.6 ± 17.6 ***P* > 0.05**	244.50 ± 47.37 ***P* > 0.05**	290.96 ± 40.66
SPAP (mmHg)	44.80 ± 5.89 ***P* > 0.05**	43 ± 1.41 ***P* < 0.001**	49.33 ± 9.18
EF%	52 ± 4.18 ***P* > 0.05**	51.50 ± 0.70 ***P* > 0.05**	48.96 ± 6.57
Cardiac output (L/min)	6.34 ± 0.16 ***P* > 0.05**	5.95 ± 0.07 ***P* < 0.001**	6.40 ± 0.58
Outcome			
Died	1(20%)	1(50%)	11(40.74%)
Survivor	4(80%)	1(50%)	16(59.25%)

Table 4 Correlations between pulmonary arterial pressure (PAP) and different variables in all studied groups.

	Hemodialysis group (No. = 65)		Peritoneal dialysis group (No. = 12)		Conservative management group (No. = 22)	
	Pearson correlation	Significance	Pearson correlation	Significance	Pearson correlation	Significance
Age	0.431	***P* < 0.001**	0.726	***P* < 0.008**	0.339	***P* > 0.05**
Duration of dialysis	0.536	***P* < 0.001**	0.780	***P* < 0.003**		
Hemoglobin (gm/dl)	−0.127	***P* > 0.05**	−0.092	***P* > 0.05**	−0.214	***P* > 0.05**
Hematocrit (%)	−0.187	***P* > 0.05**	0.374	***P* > 0.05**	0.003	***P* > 0.05**
Blood urea mg/dl	0.339	***P* < 0.006**	0.643	***P* < 0.02**	0.630	***P* < 0.002**
S. creatinine (mg/dl)	0.433	***P* < 0.001**	0.553	***P* > 0.05**	0.553	***P* < 0.008**
HCO3 (mEq/L)	−0.464	***P* < 0.001**	−0.404	***P* > 0.05**	−0.623	***P* < 0.002**
S. calcium (mg/dl)	0.086	***P* > 0.05**	−0.422	***P* > 0.05**	−0.462	***P* < 0.03**
S. phosphorus (mg/dl)	0.584	***P* < 0.001**	0.144	***P* > 0.05**	−0.247	***P* > 0.05**
PTH (pg/ml)	0.577	***P* < 0.001**	0.223	***P* > 0.05**	0.656	***P* < 0.001**
EF%	−0.369	***P* < 0.002**	0.124	***P* > 0.05**	0.046	***P* > 0.05**
Cardiac output (L/min)	0.749	***P* < 0.001**	0.757	***P* < 0.004**	0.706	***P* < 0.001**
AVF flow (ml/min.)	0.809	***P* < 0.001**				

serum parathyroid hormone, SPAP, cardiac output, and AVF flow and highly statistically significant decrease in serum HCO3, EF% in pulmonary hypertension subgroup compared to normal PAP subgroup in the hemodialysis patients and a positive significant correlation between PAP and age, duration of dialysis treatment, blood urea, serum creatinine, serum phosphorous, serum parathyroid hormone, cardiac output, and AVF flow as well as an inverse correlation between PAP, serum HCO3 and EF%. Diabetes mellitus and hypertension have a higher prevalence in the pulmonary hypertension subgroup than the normal PAP subgroup. In a similar study Havlucu et al. [4] evaluated 23 predialysis and 25 HD patients, those with elevated PAP had increased PTH levels, cardiac output values and chronic renal failure duration; AVF flow and duration were positively and residual urine volume negatively correlated with PAP. Yigla et al. [19] reported that patients with PH receiving hemodialysis had a significantly higher cardiac output (6.9 L/min vs 5.5 L/min, $p = 0.017$). Abdelwhab and Elshinnawy [11] demonstrated that Patients with PHT in the hemodialysis group have a significantly higher AVF blood flow and PAP correlates with AVF flow. Fabbian et al. [20] demonstrated that the group of subjects with PH had higher dialysis vintage (63 ± 60 versus 27 ± 32 months, $P = 0.016$), interdialytic weight gain (2.1 ± 1 versus 1.3 ± 0.9 kg, $P = 0.016$), lower diastolic blood pressure (73 ± 12 versus 80 ± 8 mmHg, $P = 0.01$) and ejection fraction (54 ± 13 versus 60 ± 7%, $P = 0.021$) than the patients with normal PAP. PAP was correlated positively with diastolic left ventricular volume ($P = 0.32$, $P = 0.013$) and negatively with ejection fraction ($r = -0.54$, $P < 0.001$). In the same group they found a higher prevalence of diabetes (18 versus 3%, $P = 0.05$). Abdallah et al. [22] demonstrated that PHT (systolic PAP = 35 mmHg) was observed in 25 (56.8%) patients receiving hemodialysis with a mean systolic PAP of 46.4 ± 13.6 mmHg. In the predialysis group after creation of AV fistula, PHT was found in 6 (42.9%) patients with a mean systolic PAP of 42.8 ± 12.8 mmHg. The cardiac output and AV shunt flow were found to be increased in patients with elevated systolic PAP in both groups ($p < 0.05$). CRF duration and AV fistula duration were positively correlated with systolic PAP in patients receiving hemodialysis ($p < 0.05$). On the other hand, Amin et al. [23] reported that there was no significant difference between patients with PH and those without PH in end-stage renal disease patients, who were receiving

regular hemodialysis with regard to age, duration of dialysis, serum calcium (9.6 ± 2 mg/dL vs 10 ± 2 mg/dL), phosphorus (6 ± 1.4 mg/L vs 6.2 ± 1.9 mg/L), alkaline phosphatase (609 ± 768 U/L vs 473 ± 574 U/L), parathyroid hormone (PTH) [420 ± 512 pg/mL vs 354 ± 519 pg/mL]. Mortality in our studied hemodialysis group was higher in the pulmonary hypertension subgroup (11 out of 27 patients (40.74%). Yigla et al., 2003 [19] reported that nine patients (15.5%) died during follow-up: six patients with PH and three patients without PH, corresponding to mortality rates of 30.4% and 8.5%, respectively in his studied patients receiving hemodialysis and peritoneal dialysis. Yigla et al. [6] demonstrated that patients with PHT evaluated by echocardiography at the beginning of HD treatment, and with PHT developing soon after HD initiation, had shorter survival than their counterparts without PHT. Our study showed a highly statistically significant increase in age, duration of dialysis treatment, blood urea, serum creatinine, SPAP, and cardiac output in pulmonary hypertension subgroup compared to normal PAP subgroup of peritoneal dialysis group and a positive significant correlation between PAP and age, duration of dialysis treatment, blood urea, and cardiac output. Etemadi et al. [24] showed no differences in gender, age, weight, duration of dialysis, calcium, phosphorus, alkaline phosphatase, albumin, parathyroid hormone level, total iron binding capacity, ferritin, creatinine and blood urea nitrogen between the patients with PAH and those with normal PAP ($P > 0.05$) in the peritoneal dialysis group. Fabbian et al. [20] demonstrated that PD patients with PHT had lower ejection fraction (45 ± 15 versus 62 ± 5%, $P = 0.003$) than those without PHT. PAP was positively correlated with diastolic left ventricular volume ($r = 0.32$, $P = 0.013$) and negatively with ejection fraction ($r = -0.54$, $P < 0.001$). Hematocrit % was statistically significantly lower and cardiac output statistically significantly higher in the hemodialysis pulmonary hypertension subgroup than both peritoneal dialysis and conservative management subgroups. Yigla et al. [19] compared data on the 23 patients with PH receiving hemodialysis with the 35 patients without PH receiving hemodialysis. The cardiac output was significantly higher among the PH subgroup (6.9 ± 1.8 L/min vs 5.5 ± 0.7 L/min, $p < 0.017$). The hemoglobin and hematocrit levels were significantly lower in the PH subgroup (9.7 ± 1 g/dL vs 10.9 ± 1.1 g/dL and 30.4 ± 2.1% vs 34.6 ± 2.5%, $p = 0.012$ and 0.007, respectively). Nissenson et al. [25] has recommended optimization of the hematocrit to maximize the blood oxygen carrying capacity and minimize the impact of arterial hypoxemia. It has been found that repeated episodes of hypoxia during and/or after HD lead to the development of pulmonary hypertension and cause morphological changes in the lung [26–28].

In the present study, the prevalence of pulmonary hypertension was highest in the HD group (41.53%), which is not surprising, as these patients had higher AV fistula flow, cardiac output, serum creatinine, and phosphorous levels; lower hemoglobin, hematocrit, serum bicarbonate values, and EF%. Brachial AVF; 23 out of 27 patients (85.18%) represent the majority of patients in the pulmonary hypertension subgroup, and radial AVF; 23 out of 38 (60.52%) represent the majority of patients in the normal PAP subgroup of our studied hemodialysis patients. It has been suggested that some factors, such as the size or the location of AVF, are involved in the mechanism that increases PAP [4]. On the contrary Tarrass et al. [29] did not find any difference in cardiac output between patients with and without PHT, and the effect of AVF location was not statistically significant. Beigi et al. [30] reported a positive correlation between mean fistula flow and PAP and as well as in our study, an inverse correlation between PAP and ejection fraction.

Study limitations

This study has certain limitations. The exclusion criteria used in our protocol resulted in a small study group, since the majority of patients with CKD had concomitant cardiac or pulmonary disease. The exclusion of patients with CKD with cardiac or pulmonary disease from analysis was a methodological necessity. Moreover, PAP was measured by a non-invasive method, Doppler echocardiography, with-out obtaining direct invasive measurements (e.g. right heart catheterization). However, measurements of PAP by the applied Doppler echocardiographic method have been reported to have a good correlation with measurements obtained by invasive methods in some studies [24,31,32]. This method of PAP measurement has been widely applied in previous studies on PAH in patients on HD or PD [2,5,19,21].

Conclusion

This study demonstrated a high prevalence of pulmonary hypertension among patients with CKD on and without dialysis. The prevalence was highest among patients with ESRD receiving long-term hemodialysis (41.53%) than those on peritoneal dialysis especially in patients with older age, longer duration of dialysis treatment, higher AV fistula flow, cardiac output, serum creatinine; lower hemoglobin, hematocrit, serum bicarbonate values, and EF% which all positively correlated with PAP and may be involved in the pathogenesis of pulmonary hypertension. Early detection of pulmonary hypertension is important in order to avoid the serious consequences of the disease, changing dialysis modality or referring for renal transplantation. Patients on peritoneal dialysis (PD) had the least prevalence of pulmonary hypertension 2/12(16.66%). Hence, it seems that PD may be better as the mode of renal replacement therapy if development of pulmonary hypertension is to be prevented.

References

[1] K.B. Martin, J.R. Klinger, S.I.S. Rounds, Pulmonary arterial hypertension: new insights and new hope, Respirology 11 (1) (2006) 6–17.
[2] A. Unal, K. Tasdemir, S. Oymak, M. Duran, I. Kocyigit, F. Oguz, et al, The long-term effects of arteriovenous fistula creation on the development of pulmonary hypertension in hemodialysis patients, Hemodial Int. 14 (2010) 398–402.
[3] M. Yigla, Z. Abassi, S.A. Reisner, F. Nakhoul, Pulmonary hypertension in hemodialysis patients: an unrecognized threat, Semin. Dial. 19 (5) (2006) 353–357.
[4] Y. Havlucu, S. Kursat, C. Ekmekci, P. Celik, S. Serter, O. Bayturan, et al, Pulmonary hypertension in patients with chronic renal failure, Respiration 74 (2007) 503–510.
[5] M. Yigla, Z. Keidar, I. Safadi, N. Tov, S.A. Reisner, F. Nakhoul, Pulmonary calcification in hemodialysis patients: correlation with pulmonary artery pressure values, Kidney Int. 66 (2004) 806–810.

[6] M. Yigla, O. Fruchter, D. Aharonson, N. Yanay, S.A. Reisner, M. Lewin, et al, Pulmonary hypertension is an independent predictor of mortality in hemodialysis patients, Kidney Int. 75 (2009) 969–975.
[7] M. Berger, A. Haimowitz, P. Van Tosh, et al, Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound, J. Am. Coll. Cardiol. 6 (1985) 359–365.
[8] H. Ihlen, K. Endresen, S. Golf, et al, Cardiac stroke volume during exercise measured by Doppler echocardiography: comparison with the thermodilution technique and evaluation of reproducibility, Br. Heart J. 58 (1987) 455–459.
[9] J. Coresh, E. Selvin, L.A. Stevens, J. Manzi, J.W. Kusek, et al, Prevalence of chronic kidney disease in the United States, JAMA 298 (2007) 2038–2047.
[10] S. Pabst, C. Hammerstingl, F. Hundt, T. Gerhardt, C. Grohe, G. Nickenig, R. Woitas, D. Skowasch, Pulmonary hypertension in patients with chronic kidney disease on dialysis and without dialysis: results of the PEPPER-study. Results of the PEPPER-study. PLoS One 7(4), e35310. doi:10.1371/journal.pone.0035310.
[11] S. Abdelwhab, S. Elshinnawy, Pulmonary hypertension in chronic renal failure patients, Am. J. Nephrol. 28 (2008) 990–997.
[12] H.W. Farber, J. Loscalzo, Pulmonary arterial hypertension, N. Engl. J. Med. 351 (2004) 1655–1665.
[13] M. Yigla, S. Dabbah, Z.S. Azzam, A.H. Rubin, S.A. Reisner, Background diseases in 671 patients with moderate to severe pulmonary hypertension, Isr. Med. Assoc. J. 2 (2000) 684–689.
[14] Z. Abassi, F. Nakhoul, E. Khankin, S.A. Reisner, M. Yigla, Pulmonary hypertension in chronic dialysis patients with arteriovenous fistula: pathogenesis and therapeutic prospective, Curr. Opin. Nephrol. Hypertens. 15 (4) (2006) 353–360.
[15] L. Kumbar, P.A. Fein, M.A. Rafiq, C. Borawski, J. Chattopadhyay, M.M. Avram, Pulmonary hypertension in peritoneal dialysis patients, Adv. Perit. Dial. 23 (2007) 127–131.
[16] S.S. Bozbas, S. Akcay, C. Altin, H. Bozbas, E. Karacaglar, S. Kanyilmaz, et al, Pulmonary hypertension in patients with end-stage renal disease undergoing renal transplantation, Trans. Proc. 41 (2009) 2753–2756.
[17] A. Domenici, R. Luciani, F. Principe, Pulmonary hypertension in dialysis patients, Perit. Dial. Int. 30 (2) (2010) 251–252.
[18] P. Patel, G. Abraham, B. Pratap, R. Ramalakshmi, M. Mathew, J.M. Jeevan, T.R. Muralidharan, A. Moorthy, N. Leslie, Clinical and biochemical parameters in chronic kidney disease with pulmonary hypertension, Indian J. Nephrol. 17 (2007) 4–6.
[19] M. Yigla, F. Nakhoul, A. Sabag, N. Tov, B. Gorevich, Z. Abassi, S.A. Reisner, Pulmonary hypertension in patients with end-stage renal disease, Chest 123 (5) (2003) 1577–1582.
[20] F. Fabbian, S. Cantelli, C. Molino, M. Pala, C. Longhini, F. Portaluppi, Pulmonary hypertension in dialysis patients: a cross-sectional italian study. Int. J. Nephrol. 2011 (2011), Article ID 283475.
[21] M. Mahdavi-Mazdeh, S. Alijavad-Mousavi, H. Yahyazadeh, M. Azadi, H. Yoosefnejad, Y. Ataiipoor, Pulmonary hypertension in hemodialysis patients, Saudi J. Kidney Dis. Transpl. 19 (2008) 189–193.
[22] Abdallah Emad, Waked Emam, Metwaly Amna, Khalek Ashraf, The role of arterio-venous shunt in the pathogenesis of pulmonary hypertension in patients with end-stage renal disease, Kidney 19(5) (2010) 239.
[23] M. Amin, A. Fawzy, M. Abdel Hamid, A. Elhendy, Pulmonary hypertension in patients with chronic renal failure. role of parathyroid hormone and pulmonary artery calcifications, Chest 124 (6) (2003) 2093–2097.
[24] J. Etemadi, H. Zolfaghari, R. Firoozi, M.R. Ardalan, M. Toufan, M.M. Shoja, K. Ghabili, Unexplained pulmonary hypertension in peritoneal dialysis and hemodialysis patients, Rev. Port Pneumol. (2011), http://dx.doi.org/10.1016/j.rppneu.2011.07.002.
[25] A.R. Nissenson, R.N. Fine, in: A.R. Nissenson, R.N. Fine (Eds.), Dialysis Therapy, third ed., Hanley and Belfus, California, 2001, p. 98–99.
[26] M.P. Dhakal, M.C. Kallay, M.A. Shelly, T.E. Taley, Post-hemodialysis hypoxia occurs in both biocompatible and bioincompatible dialyzers, Dialysis Transplant 28 (1999) 666–672.
[27] N.M. Aurigemma, N.T. Feldman, M. Gottlieb, R.H. Ingram Jr, J.M. Lazarus, E.G. Lowrie, Arterial oxygenation during hemodialysis, N. Engl. J. Med. 297 (1977) 871–873.
[28] H. Igarishi, A. Kiois, F. Gejyo, M. Arakawa, Physiologic approach to dialysis induced hypoxemia, Nephron 41 (1985) 62–69.
[29] F. Tarrass, M. Benjelloun, G. Medkouri, K. Hachim, M.G. Benghanem, B. Ramdani, Doppler echocardiograph evaluation of pulmonary hypertension in patients undergoing hemodialysis, Hemodialysis Int. 10 (4) (2006) 356–359.
[30] A.A. Beigi, A.M.M. Sadeghi, A.R. Khosravi, M. Karami, H. Masoudpour, Effects of the arteriovenous fistula on pulmonary artery pressure and cardiac output in patients with chronic renal failure, J. Vasc. Access 10 (3) (2009) 160–166.
[31] H.W. Farber, A.J. Foreman, D.P. Miller, M.D. McGoon, REVEAL registry: correlation of right heart catheterization and echocardiography in patients with pulmonary arterial hypertension, Congest Heart Fail 17 (2011) 56–64.
[32] S. Marangoni, A. Quadri, A. Dotti, S. Scalvini, M. Volterrani, M. Schena, et al, Noninvasive assessment of pulmonary hypertension: a simultaneous echo-Doppler hemodynamic study, Cardiology 75 (1988) 401–408.