Pulmonary Hypertension and Predisposing Factors in Patients Receiving Hemodialysis

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Introduction. The aim of this study was to evaluate the frequency of unexplained pulmonary hypertension (PHT) among patients on hemodialysis at 2 centers and to evaluate possible predisposing factors.

Materials and Methods. In this cross-sectional study, PHT was screened by Doppler echocardiography on the day after dialysis in 62 patients with end-stage renal disease receiving maintenance hemodialysis via arteriovenous access. Pulmonary hypertension was defined as a systolic pulmonary arterial pressure (PAP) higher than 35 mm Hg, and the systolic PAP was calculated using the modified Bernoulli equation. Clinical variables were compared between patients with and without PHT.

Results. A PAP higher than 35 mm Hg was found in 32 patients (49.3%) receiving hemodialysis, with a mean systolic PAP of 39.58 ± 13.27 mm Hg. Blood hemoglobin level was significantly lower in the patients with PHT than those without PHT (9.8 ± 1.97 g/dL versus 11.07 ± 1.86 g/dL; P = .01). In addition, serum levels of albumin was lower in these patients (3.38 ± 0.32 g/dL versus 3.75 ± 0.44 g/dL; P = .02).

Conclusions. This study demonstrates a surprisingly high prevalence of PHT among patients with end-stage renal disease receiving hemodialysis. We concluded that the best approach to this unrecognized complication that is associated with reduced survival is keeping it in mind and looking for it in the management of patients on dialysis.

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INTRODUCTION

Excess mortality rates due to cardiovascular diseases in patients with end-stage renal disease (ESRD) has been described by epidemiological and clinical studies.[1] Although controversial, this may be due in part to the presence of excess vascular calcification which can be observed even in very young patients who receive dialysis.[2] Vascular calcification, the most common type of extra-osseous calcification in ESRD, is not a new issue, but noninvasive techniques have increased our ability to detect it today.[2-4] A current hypothesis is that by widely using calcium-containing oral phosphate binders helping order to prevent uremic osteodystrophy, we have unwittingly accelerated uremic vasculopathy. This has resulted in vascular stiffness in patients on dialysis, thereby markedly contributing to premature cardiovascular mortality.[5]

On the other hand, it is also possible that the state of secondary hyperparathyroidism in patients with chronic kidney disease is responsible

for the development of pulmonary arterial calcification (PAC). It has been suggested that the abnormalities in right ventricular function in patients with ESRD are largely due to pulmonary hypertension (PHT), which develops secondary to PAC. This unrecognized complication of hemodialysis therapy with reduced survival is not uncommon, and it presents as an extremely serious disease that is difficult to identify early owing to the insidious nature of the early-stage symptoms. It seems that heightened awareness among patients at risk of early-stage disease manifestation is necessary to allow for diagnosis before significant pathophysiological changes.[6] Regardless of the etiology, the morbidity and mortality of long-standing PHT exceed compared to those expected from the causative condition. Pulmonary arterial pressure (PAP) may be further increased by high cardiac output resulting from the arteriovenous access itself, worsened by commonly occurring anemia and fluid overload.[7,8] Doppler echocardiography has enabled noninvasive accurate estimation of systemic PAP.[9] The aim of this study was to evaluate the frequency of PHT in patients on maintenance hemodialysis therapy and to examine some possible etiologic factors for its occurrence.

MATERIALS AND METHODS

Patient Selection

The original study population included patients with ESRD on maintenance hemodialysis therapy via surgically created native arteriovenous fistula or graft. They were on dialysis 3 times per week in 4-hour sessions at 2 dialysis centers of Shaheed Hasheminejad Hospital and Imam Khomeni Hospital. The project was approved by the research deputy of Iran University of Medical Sciences. Patients with comorbid conditions and those with PHT most probably secondary to their cardiac disease, pulmonary disease, or collagen-vascular disease were excluded. The study group consisted of 68 eligible patients without a known cause of PHT. Six of them refused to participate in the study and 62 who provided informed consent were in the final study group.

Patient Evaluation

Systolic PAP was estimated in the 62 patients receiving hemodialysis by Doppler echocardiography. Echocardiography study in the patients was performed on the day after dialysis. One experienced cardiologist performed all the echocardiographic studies, using a Megas ultrasound machine (Biosound Esaote, Indianapolis, USA). A complete 2-dimensional Doppler echocardiographic study was obtained on each patient. A tricuspid regurgitation systolic jet was recorded from the parasternal or apical window with the continuous-wave Doppler echocardiographic probe. Pulmonary hypertension was defined as a systolic PAP higher than 35 mm Hg, and the systolic right ventricular pressure (or PAP) was calculated using the modified Bernoulli equation, in which the estimated right atrial pressure was assumed to be 15 mm Hg for dilated right atriums and 10 mm Hg for normal or slightly enlarged right atriums:

PAP = tricuspid systolic jet + estimated right atrial pressure

The patient's general data (age, sex, comorbidities, and medications used) and data regarding the kidney disease, including etiology of kidney failure, age at onset, duration of hemodialysis therapy, and access and type location (brachial or radial) were recorded. Data on blood tests for hemoglobin, hematocrit, calcium, phosphorus, and parathyroid hormone levels were collected as well. For this purpose, the mean of values obtained the past two months were utilized. Patients with PHT were evaluated further by an experienced pulmonologist to uncover other potential causes of PHT. This assessment included history, physical examination, chest radiography, chest computed tomography, and complete pulmonary function tests.

Analyses of Data

The frequency of PHT was calculated in patients with ESRD on maintenance hemodialysis and the clinical variables were compared between patients with and without PHT using the *t* test and the chi-square test, where appropriate. Values of the numeral variables were expressed as mean ± standard deviation. *P* values less than .05 were considered significant.

RESULTS

The PAP values of the patients are presented in Table 1. The mean duration of hemodialysis therapy prior to the echocardiography study was 78.6 ± 73.8 months. The most common etiologies

Table 1. Systolic PAP in Patients on Hemodialysis*

Parameter	Value
Number of patients	62
Mean of PAP (range), mm Hg	39.58 ± 13.27 (17 to 75)
Patients with PAP > 36 mm Hg and ≤ 45 mm Hg (%)	15 (23.1)
Patients with PAP > 46 mmHg (%)	17 (26.2)

*PAP indicates pulmonary arterial pressure.

of kidney failure were diabetes mellitus and arterial hypertension. Pulmonary hypertension was observed in 32 patients receiving hemodialysis (49.3%) with a mean systolic PAP of 39.58 ± 13.27 mm Hg. Characteristics of the patients with and without PHT are presented in Table 2. The mean blood hemoglobin and serum albumin levels were significantly lower in the patients with PHT. Although ejection fraction was significantly higher in the patients with PHT, it was not clinically important.

The elevated ejection fraction in both groups could not be explained by the hemoglobin level as a covariant (Figures 1 and 2). The difference in duration of hemodialysis therapy was not significant between the patients with and without PHT subgroup (78.2 months versus 80.7 months, respectively). Other variables, including anatomic location of the dialysis vascular access, lipid profile, parathyroid hormone activity, and calcium-phosphorus product did not differ significantly between the two groups.

DISCUSSION

The reported prevalence of PHT in patients on maintenance hemodialysis is 26% to 40% as

Table 2. Clinical and Laboratory Data in Patients With Normal PAP Versus Patients With High PAP*

Variables	Patients on Hemodialysis		*P*
	Normal PAP	High PAP	
Number of patients	30	32	
Mean age, y	53.5 ± 16.3	51.1 ± 17.3	.58
Sex			.21
Male	17 (56.7)	13 (43.3)	
Female	13 (40.6)	19 (59.4)	
Mean ejection fraction, %	52.2 ± 7.2	46.3 ± 11.7	.02
Mean hemoglobin, g/dL	11.07 ± 1.86	9.8 ± 1.97	.01
Mean parathyroid hormone activity (range), IU	275.3 ± 151.6 (40 to 498)	279.57 ± 128.40 (38 to 500)	.92
Mean calcium-phosphorus product (range), mg^2/dL^2	58.27 ± 14.74 (33.6 to 91.3)	56.22 ± 12.76 (32.0 to 80.1)	.57
Mean albumin (range), g/dL	3.75 ± 0.44 (3.1 to 5.0)	3.38 ± 0.32 (2.8 to 3.8)	.02

*Values in parentheses are percents unless otherwise indicated. PAP indicates pulmonary arterial pressure.

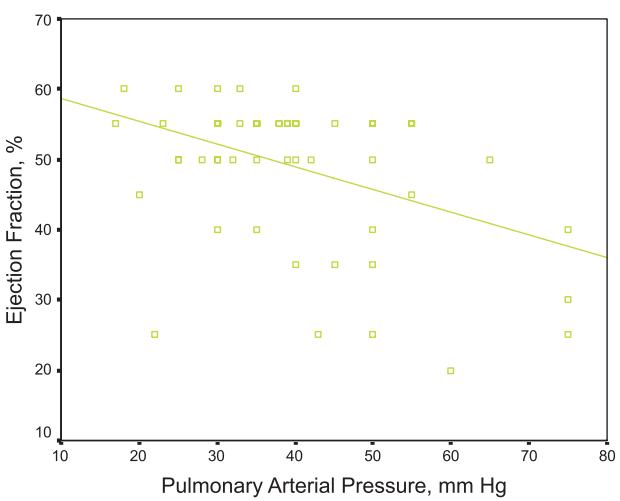

Figure 1. Correlation between pulmonary arterial pressure and ejection fraction (*P* = .001).

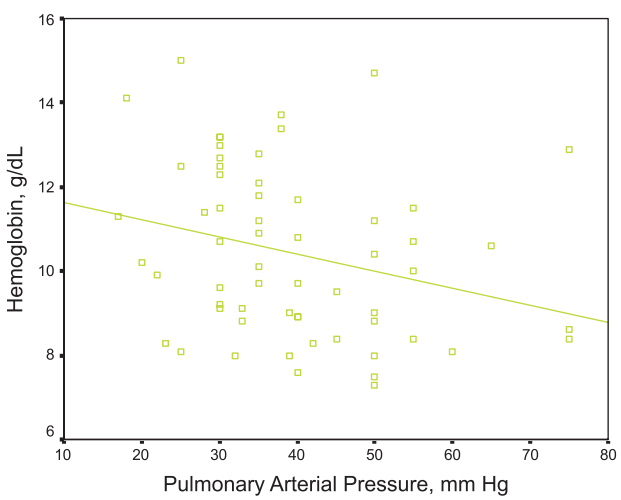

Figure 2. Correlation between pulmonary arterial pressure and blood hemoglobin (*P* = .03).

detected by Doppler echocardiography in different studies.[4,7,10-12] In this study, the frequency of PHT as defined by Doppler echocardiographic assessment of the tricuspid valve was almost 50% (mean systolic PAP, 39.58 ± 13.27 mm Hg). In 17 patients (26%), PHT was moderately severe (PAP, greater than 45 mm Hg). The patients with PHT had significantly lower blood hemoglobin and albumin levels which may be a confounding factor and the reason of our higher rate of PHT frequency. We could not show any difference in age, duration of dialysis, and lipid profile.[4,10]

Increased stiffness of the pulmonary capillaries due to hyperparathyroidism and pulmonary vascular calcification is one possible explanation for PHT in patients with ESRD. Akmal and colleagues studied the role of excess parathyroid hormone in the genesis of pulmonary calcifications in dogs with experimental chronic kidney failure. They proposed that the abnormalities in right ventricular function are in large due to pulmonary hypertension which develops secondary to pulmonary calcification as ESRD is associated with generalized calcification.[4,13] We previously reported that only 1.8% and 34.2% of the patients on hemodialysis achieved 4 and 3 target levels of laboratory tests defined by the National Kidney Foundation Dialysis Outcomes Quality Initiative guidelines, respectively.[14] Subsequently, it is expected that most patients with calcium-phosphorus metabolism abnormalities reveal higher pulmonary arterial pressure. Surprisingly, in the present study, parathyroid hormone activity and calcium-phosphorus product did not differ significantly between the patients with and without PHT. It is possible that other pathophysiologies play a role.

A theory by Barak and Katz explains that microbubbles originating from the dialysis tubes or filter flow in the venous vasculature are trapped in the pulmonary circulation. Thus, the patient on hemodialysis may suffer lung injury due to a microbubble shower. In a chronic course, the recurrent ongoing microbubble-induced inflammatory response and lung injury may explain the high pulmonary morbidity, manifested as increased pulmonary artery pressure, of patients on long-term dialysis.[15] The fact that endothelial dysfunction is a key element of the manifestation of disease pathophysiology, marked by prolonged elevation of endothelin (a powerful mitogen) coupled with chronic reductions in nitric oxide and prostaglandin 2, strongly supports this theory.[7,16]

Yigla and coworkers mentioned that the impact of large arteriovenous access on the pulmonary circulation has not been studied extensively. They suggested in their comprehensive studies that pathologic elevation of PAP occurs in those patients whose pulmonary circulation cannot compensate for the arteriovenous access-related high cardiac output. They recommend surgical reduction of oversized arteriovenous accesses should be considered in patients with PHT and extremely high cardiac output who demonstrate reduction of both cardiac output and PHT following temporary closure of their arteriovenous access.[7,16]

CONCLUSIONS

Based on the data presented, we concluded that a substantial number of uremic patients have functional abnormality of pulmonary circulation. This unrecognized complication of maintenance hemodialysis therapy is not uncommon, and perhaps most importantly, is associated with reduced survival. Therefore, the best approach to the disease is looking for it. It is suggested to design studies to evaluate the impact of arteriovenous fistula on the PAP in pre-ESRD period. In this context, volume expansion on the day after dialysis and anemia cannot be serious confounding factors.

CONFLICT OF INTEREST

None declared.

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