PULMONARY HYPERTENSION IN CKD PREDIALYSIS PATIENTS WITH PRESERVED LEFT VENTRICULAR FUNCTION

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Introduction:

Pulmonary hypertension (PH) is highly prevalent among patients undergoing hemodialysis or peritoneal dialysis increasing cardiovascular morbidity and mortality1. Factors such as chronic volume overload, anemia and creation of an arterio-venous fistula contribute to the development of increased right heart-sided pressures2. However, in earlier stages of CKD data about the prevalence of PH, underlying pathophysiology and its relation with markers of renal disease are limited.

Aim of the study

To evaluate the prevalence of pulmonary hypertension among patients suffering from CKD stage 3 and 4 and its relation with various biochemical parameters of renal function.

Patients and methods :

Thirty three CKD stage 3 and 4 patients (eGFR 60-15 ml/min/1,73 m2), 16 male and 17 female, aged 74.4±6.9 years, were enrolled in the study. Primary renal disease was diabetic nephropathy and hypertensive nefroangiosclerosis in 14 and 8 patients, respectively. The rest of the patients suffered from other renal disease or from renal failure of unknown origin. Inclusion criteria were preserved left ventricular systolic function (EF>55%) and absence of secondary pulmonary hypertension. Patients suffering from heart failure with EF<55%, chronic parenchymal or vascular pulmonary disease or connective tissue disease were excluded. We recorded demographic data, medications, biochemical and several hormonal parameters (creatinine, iPTH, calcium, phosphorus, Ca×P product, 25OH vitamin D, CRP, Hb and ferritin). Albuminuria was measured in a 24-hour urine collection and glomerular filtration rate was estimated by using the four-variable MDRD equation. Systolic pulmonary artery pressure (sPAP) was calculated using the modified Bernoulli equation (PAP=4×(tricuspid systolic jet)2+10 mmHg). Values of sPAP >35 mm Hg were considered indicative of pulmonary hypertension. We also measured LVEF, Sa (RV) (cm/sec), E/E' and CO (L/min).

We evaluated the correlation between various cardiac and biochemical parameters in patients with pulmonary hypertension with simple regression analysis and comparatively between patients with or without pulmonary hypertension using Student's unpaired t-test. Statistically significance was set at p<0,05.

Results:

Pulmonary hypertension was found in thirteen out of thirty-three CKD patients, 4 males and 9 females of mean age 76,2 years (group high PAP). Twenty patients, 12 males and 8 females of mean age 73,2 years had normal values of sPAP (group normal PAP). The patients in normal PAP group presented significantly higher values of eGFR 37,9±14,4 ml/min/1,73 m2 vs 28,5±9,9ml/min/1,73 m2 in high PAP group (p<0,04). Moreover a significant correlation was found in all studied patients between eGFR levels and degree of PAP (r=0.34, p<0.04) (Table 1).

Although there was a significant difference in systolic pulmonary artery pressure between the two groups (41,7±8,9 mmHg vs 20,2±8 mmHg, in the high and normal PAP group respectively, p<0,0001), the cardiac indexes Sa (RV), E/E' and CO were not statistically different (Table 2).

Analysis of biochemical parameters of bone and mineral metabolism showed no difference between the two groups with regard to the levels of calcium, phosphorus, Ca×P product and 25OH vitamin D. On the contrary, CKD patients with pulmonary hypertension had significantly higher values of iPTH 174±107 pg/ml vs 99±48 pg/ml (p<0,02) (Table 3). No difference was found regarding the rest of hematological and biochemical parameters (Hb, ferritin, CRP) as well as the EPO dose between the two groups.

Patients with increased sPAP had overt albuminuria while in the group with normal sPAP most of the patients were within microalbuminuric levels (827±974 mg/24h vs 330±370mg/24h respectively, p<0,004) (Table 3). Furthermore, a significant correlation between sPAP and albuminuria (p<0.04) was found.

Discussion:

Pulmonary hypertension (PH) may be idiopathic or secondary to a variety of diseases (i.e. connective tissue, left-sided heart dysfunction, chronic obstructive or restrictive lung diseases) and is classified in 5 classes according to its specific etiology3. Definition of PH presupposes right-sided heart catheterization and values of mean pulmonary artery pressure ≥25mmHg at rest4. Alternatively, sPAP can be measured by Doppler echocardiography, based on tricuspid regurgitation jet, by using the modified Bernoulli equation5.

The prevalence of PH in the general population has been estimated in about 5%6. In predialysis CKD patients the reported prevalence of PH ranges from 9-39% and increases to 18,8-68,8% in dialysis patients2. In our study the prevalence of PH was 39% (13/33), coinciding with the upper value of the reported range.

CKD is classified in the fifth group of diseases which may cause PH. This group includes several forms of PH with multifactorial or unclear etiology3. Patients with CKD present a variety of risk factors which favor the development of pulmonary vascular resistance. In our cohort of predialysis patients a significant correlation was observed between eGFR levels and degree of PAP, suggesting that decline in renal function is associated with increment of sPAP. Progressive decline of renal function is associsted with complications such as volume overload, anemia or secondary hyperparathyroidism which contribute to the development of pulmonary hypertension.

We report a significant difference in the values of iPTH between the two studied groups. This observation indicates that secondary hyperparathyroidism could be implicated in the development of PH. Experimentally, calcifications of pulmonary arteries and arterioles in the context of secondary hyperparathyroidism increases PH7. However, data from clinical studies in humans do not consistently confirm this association8,9.

Moreover, we noticed a significant correlation of increased sPAP with the level of albuminuria. This correlation has also been observed in patients with PH secondary to sickle cell disease10. Albuminuria, a hallmark of renal disease, is also an independent risk factor for cardiovascular morbidity and mortality11.

A common underlying pathophysiologic process could explain an association between albumin excretion and increased pulmonary artery pressure. Pulmonary vasoconstriction due to impaired endothelial function is an early pathogenetic event in the course of development of PH. Imbalance between vasoconstrictory (i.e.endothelin 1) and vasodilatory substances (i.e. NO) leads to dysregulation of normal vascular tone12. Generalized endothelial dysfunction accompanies diabetic microalbuminuria13. Overt albuminuria has been associated with decreased NO activity14 and high levels of asymmetric dimethylarginine, an endogenous inhibitor of NO15, also suggesting impaired endothelial function. Generalized endothelial injury leading to increased microvascular permeability with albumin loss at the glomerular level16 and increased pulmonary vasoconstriction could represent a link between CKD and PH progression.

Conclusion:

Pulmonary hypertension is frequent among our predialysis patients with preserved left ventricular function. Decline in renal function is associated with increment of sPAP. Although a significant correlation was observed between sPAP with iPTH and the urine albumin excretion further studies needed to confirm and elucidate the underlying mechanisms of these associations.

Table 1. Demographic data of two groups of patients

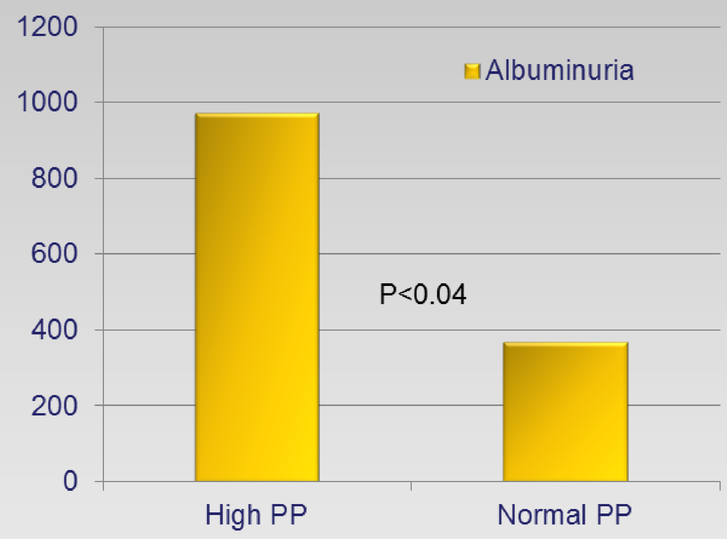
	High PAP	Normal PAP	p
Patients (%)	13 (39%)	20 (61%)	
Gender (M/F)	4 M/9 F	12 M/8 F	
Mean age (years)	76,2±5,8	73,2±7,5	
eGFR(ml/min)	28,5±9,9	37,9±14,4	<0,04
BMI (kg/m2)	27±3,7	28,4±5,3	N.S.

Table 2. sPAP and other cardiac indexes between the two groups

	High PAP	Normal PAP	p
sPAP (mmHg)	41,7±8,9	20,2±8	<0,0001
Sa (RV) (cm/sec)	17,4±6,8	16,6±5	N.S.
E/E'	6,8±3,9	5,9±5,3	N.S.
CO (L/min)	6±7,7	4,8±1,5	N.S.

Table 3. Levels of PTH, 25OHvitamin D and albuminuria in patients with and without pulmonary hypertension

	High PAP	Normal PAP	p
iPTH (pg/ml)	174±107	99±48	<0,02
25OH vit D (pg/ml)	24,1±11,1	27,4±8,6	N.S.
Albuminuria (mg/24h)	827±974	330±370	<0,04



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