

## Clinical Study

# Pulmonary Hypertension in Dialysis Patients: A Cross-Sectional Italian Study

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Received 31 July 2010; Accepted 26 August 2010

Academic Editor: Mitchell H. Rosner

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**Introduction.** Pulmonary hypertension (PHT) is an independent predictor of mortality. The aim of this study was to relate pulmonary arterial pressure (PAP) to the cardiovascular status of dialysis patients. **Methods.** 27 peritoneal dialysis (PD) and 29 haemodialysis (HD) patients ( $60 \pm 13$  years, 37 males, dialysis vintage was  $40 \pm 48$  months) had PAP measured by echocardiography. Clinical and laboratory data of the patients were recorded. **Results.** PHT (PAP > 35 mmHg) was detected in 22 patients (39%; PAP  $42 \pm 6$  mmHg) and was diagnosed in 18.5% of PD patients and 58.6% of HD patients ( $P = .0021$ ). The group of subjects with PH had higher dialysis vintage ( $63 \pm 60$  versus  $27 \pm 32$  months,  $P = .016$ ), interdialytic weight gain ( $2.1 \pm 1$  versus  $1.3 \pm 0.9$  Kg,  $P = .016$ ), lower diastolic blood pressure ( $73 \pm 12$  versus  $80 \pm 8$  mmHg,  $P = .01$ ) and ejection fraction ( $54 \pm 13$  versus  $60 \pm 7\%$ ,  $P = .021$ ) than the patients with normal PAP. PAP was correlated positively with diastolic left ventricular volume ( $r = 0.32$ ,  $P = .013$ ) and negatively with ejection fraction ( $r = -0.54$ ,  $P < .0001$ ). PHT was independently associated with dialysis vintage (OR 1.022, 95% CI 1.002–1.041,  $P = .029$ ) and diastolic blood pressure (OR 0.861, 95% CI 0.766–0.967,  $P = .011$ ). **Conclusions.** PHT is frequent in dialysis patients, it appears to be a late complication of HD treatment, mainly related to cardiac performance and cardiovascular disease history.

## 1. Introduction

Pulmonary hypertension (PHT) is a progressive disorder complicating heart, lung, or systemic diseases, with increased morbidity and mortality regardless of its etiology [1]. Recently it has been found that PHT is a strong independent predictor of mortality in haemodialysis (HD) patients [2]. In patients with end-stage renal disease (ESRD), PHT has been recognized to be a frequent condition and it appears to be independent from cardiovascular disease prevalence [2]. In a recent review, the prevalence of PHT in ESRD patients was reported to be around 40%–50% [3]. Its frequency has been reported to be higher in HD patients than in peritoneal dialysis (PD) ones due to the presence of arteriovenous fistula (AVF) [4, 5]. Clinical features associated with PHT in ESRD are still a matter of debate, therefore, we evaluated clinical characteristics associated with high pulmonary arterial pressure (PAP) measured by echocardiography in a group of Italian dialysis patients.

## 2. Subjects and Methods

Between January 2007 and June 2007, 56 dialysis patients underwent PAP measurement by echocardiography (age  $60 \pm 13$  years, dialysis vintage  $40 \pm 48$  months). They were selected from a population of 127 subjects dialysing in a single centre because they accepted to undergo echocardiography. Twenty nine were on HD treatment via surgically created native AVF and 27 were on PD therapy. Glomerulonephritis was the commonest cause of uraemia ( $n = 23$ ), ischaemic renal disease, cystic disease and interstitial nephritis were the renal diagnosis in 8 cases, respectively, 6 patients had diabetic nephropathy whereas 3 had undetermined renal diagnosis. Patients with chronic obstructive lung disease, chest wall or parenchymal lung disease, previous pulmonary embolism, collagen vascular disease, systemic lupus erythematosus were excluded.

The following demographic and clinical data were derived from clinical records: age, duration of dialysis

treatment, smoking and diabetes history. The increase in weight during the interdialytic time (interdialytic weight gain), systolic and diastolic blood pressure (BP) were averaged from values recorded at the beginning of dialysis sessions during the month preceding the date of echocardiography. BP measurements were performed according to guidelines [6]. Mean dry weight of each subject was averaged from the values recorded at the end of the dialysis sessions during the same period. Average levels of calcium, phosphate, parathyroid hormone (PTH, measured as intact molecule by radioimmunoassay), haemoglobin, haematocrit measured at least twice in the study period were calculated. Weekly dose of erythropoietin and calcium-phosphate product were also calculated. Ischaemic heart disease was defined either from history of myocardial infarction and/or angina associated to ischaemic changes on electrocardiogram, or by positive results at either electrocardiographic ergometry, dipyradamole scintigraphy, or dobutamine echocardiography. History of previous TIA or stroke defined cerebrovascular disease. History of claudication, amputation or presence of ischaemic lesions of lower limb extremities defined peripheral vascular disease. History of parathyroidectomy was also recorded.

Echocardiography was performed the day after a dialysis session when the patient had reached the “dry weight” prescribed by nephrologists on the clinical examination, in order to avoid clinical evident fluid overload. One experienced cardiologist performed all examinations using an Acuson Sequoia, 512 (Mountain View, CA, USA) ultrasound machine.

Every patient underwent a complete two-dimensional and Doppler echocardiography study.

Systolic pulmonary artery (PAP) pressure was calculated using the modified Bernoulli equation given by:  $PAP = 4 \times (\text{tricuspid systolic jet})^2 + 10 \text{ mm Hg}$  (estimated right atrial pressure) [7]. According to Yigla et al. [2] PHT was defined as a systolic PAP > 35 mmHg. Diastolic left ventricular volume, ejection fraction, mitral and aortic valve stenosis or incompetence were also derived from echocardiographic studies. Local ethics committee approved this observational study. The study was conducted according to the Declaration of Helsinki.

### 3. Statistical Analysis

Data are expressed as mean  $\pm$  standard deviation and as percentage when the parameter was categorical. Patients were investigated dividing PD and HD subjects with and without PHT. Difference between groups were compared with Student's *t*-test for parametric continuous variables, Mann-Witney-U test for nonparametric 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 echocardiographic parameters. Multiple logistic regression analysis was performed considering presence/absence of PHT as dependent variable, whilst all the variables that resulted statistically different in the univariate analysis, were considered as independent ones. A *P* value <.05 was used as

TABLE 1: Data describing the 56 patients in whom pulmonary artery pressure was evaluated.

Age (year)	60 $\pm$ 13
Dialysis vintage (months)	40 $\pm$ 48
Dry weight (kg)	68,5 $\pm$ 15
Interdialytic weight gain (kg)	1,6 $\pm$ 1
Systolic blood pressure (mmHg)	132 $\pm$ 20
Diastolic blood pressure (mmHg)	77 $\pm$ 11
Calcium (mg/dl)	9 $\pm$ 1
Phosphate (mg/dl)	5 $\pm$ 1
Calcium-phosphate product (mg <sup>2</sup> /dl <sup>2</sup> )	48 $\pm$ 15
PTH (pg/ml)	344 $\pm$ 340
Haemoglobin (gr/dl)	11,3 $\pm$ 1,4
Haematocrit (%)	35 $\pm$ 5
Erythropoietin (IU/week)	7243 $\pm$ 8752
Left ventricular Diastolic Volume (ml)	116 $\pm$ 33
Ejection Fraction (%)	58 $\pm$ 10
PAP (mmHg)	33 $\pm$ 8

the thresholds of statistical significance. All analyses were performed using StatView for windows.

### 4. Results

Characteristics of the 56 patients investigated are summarized in Table 1, 22 of them had PHT (39%), their mean age was 66  $\pm$  13 years and 37 were males.

Five (18.5%) in the PD group and 17 (58.6%) in the HD one had PAP > 35 mmHg (*P* = .0021). Clinical and biochemical data of the 22 patients with PHT (PAP 42  $\pm$  6 mmHg) compared with the 34 patients without PH (28  $\pm$  3 mmHg) are shown in Tables 2 and 3. The mean duration of dialysis therapy was significantly longer (63  $\pm$  60 versus 27  $\pm$  32 months, *P* = .0105) and interdialytic weight gain was higher (2.0  $\pm$  1 versus 1.3  $\pm$  0.9 Kg, *P* = .0168) in the PHT group than in group with normal PAP. On the contrary diastolic blood pressure (73  $\pm$  12 versus 80  $\pm$  8 mmHg, *P* = .01) and ejection fraction (54  $\pm$  13 versus 60  $\pm$  7%, *P* = .021) were lower in PHT patients than in subjects with normal PAP. In the same group we found higher prevalence of diabetes (18 versus 3%, *P* = .05) and mitral incompetence (100 versus 79%, *P* = .02).

PD patients with PHT had higher prevalence of diabetes (40 versus 0% *P* = .0021), aortic incompetence (100 versus 45%, *P* = .0267), higher systolic blood pressure (154  $\pm$  29 versus 129  $\pm$  13 mmHg, *P* = .0074) and lower ejection fraction (45  $\pm$  15 versus 62  $\pm$  5%, *P* = .0003) than those without PHT. HD patients with PHT had higher prevalence of smoking history (76 versus 41%, *P* = .0571) and lower diastolic blood pressure (69  $\pm$  11 versus 79  $\pm$  8 mmHg, *P* = .0196) than those without PHT.

PAP was correlated positively with diastolic left ventricular volume (*r* = 0.32, *P* = .013) negatively with ejection fraction (*r* = -0.54, *P* < .0001).

TABLE 2: Clinical and laboratory data of patients with and without pulmonary hypertension.

	PAP $\leq$ 35 ( <i>n</i> = 34)	PAP > 35 ( <i>n</i> = 22)	<i>P</i>
Age (year)	59 $\pm$ 14	61 $\pm$ 12	ns
Male/Female ( <i>n</i> (%))	22/12	15/7	ns
Diabetes ( <i>n</i> (%))	1 (3%)	4 (18%)	0.05
Smoking history ( <i>n</i> (%))	19 (56%)	17 (77%)	ns
Dialysis vintage (months)	27 $\pm$ 32	63 $\pm$ 60	0.0105
Dry weight (kg)	70 $\pm$ 16	65 $\pm$ 13	ns
Interdialytic weight gain (kg)	1,3 $\pm$ 0,9	2,0 $\pm$ 1.0	0.0168
Systolic blood pressure (mmHg)	132 $\pm$ 15	132 $\pm$ 27	ns
Diastolic blood pressure (mmHg)	80 $\pm$ 8	73 $\pm$ 12	0.0102
Calcium (mg/dl)	8,9 $\pm$ 1	9 $\pm$ 1	ns
Phosphate (mg/dl)	5,2 $\pm$ 1,7	5,2 $\pm$ 0,9	ns
Calcium-phosphate product (mg <sup>2</sup> /dl <sup>2</sup> )	48 $\pm$ 18	48 $\pm$ 10	ns
PTH (pg/ml)	316 $\pm$ 313	388 $\pm$ 381	ns
Haemoglobin (gr/dl)	11,4 $\pm$ 1,5	11 $\pm$ 1,4	ns
Haematocrit (%)	36 $\pm$ 5	34 $\pm$ 5	ns
Erythropoietin (IU/week)	5980 $\pm$ 7664	9272 $\pm$ 10015	ns

TABLE 3: Cardiovascular condition of patients with and without pulmonary hypertension.

	PAP $\leq$ 35 ( <i>n</i> = 34)	PAP > 35 ( <i>n</i> = 22)	<i>P</i>
Hypertension history ( <i>n</i> (%))	29 (85%)	17 (77%)	ns
Ischaemic heart disease ( <i>n</i> (%))	11 (32%)	10 (45%)	ns
Cerebrovascular disease ( <i>n</i> (%))	8 (24%)	5 (23%)	ns
Peripheral vascular disease ( <i>n</i> (%))	11 (32%)	6 (27%)	ns
Parathyroidectomy history ( <i>n</i> (%))	4 (12%)	0 (0%)	ns
Left ventricular hypertrophy ( <i>n</i> (%))	25 (74%)	15 (68%)	ns
Left ventricular Diastolic Volume (ml)	110 $\pm$ 32	124 $\pm$ 33	ns
Ejection Fraction (%)	60 $\pm$ 7	54 $\pm$ 13	0.0216
Mitral stenosis ( <i>n</i> (%))	1 (3%)	1 (5%)	ns
Mitral incompetence ( <i>n</i> (%))	27 (79%)	22 (100%)	0.02
Aortic stenosis ( <i>n</i> (%))	1 (3%)	3 (14%)	ns
Aortic incompetence ( <i>n</i> (%))	17 (50%)	15 (68%)	ns

In the whole population multiple logistic regression analysis showed an independent association between PHT and dialysis vintage (Odds Ratio 1.022 (95% CI 1.002–1.041) ( $P = .0297$ )) and diastolic blood pressure (Odds Ratio 0.861 (95% CI 0.766–0.967) ( $P = .0116$ );  $R^2 = 0.328$ ).

## 5. Discussion

This is a cross-sectional study investigating a small number of dialysis patients dealing with a underconsidered clinical problem. Yigla et al. [2] 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. The mechanisms involved in PHT development are still under investigation, but it has been reported that HD patients with PHT show a significantly higher cardiac output than HD patients with normal PAP [3, 4]. It has been suggested that some factors, such as the size or the location of AVF, are involved in the mechanism that increases PAP. On the contrary Tarrass et al. [8] 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. [9] 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. Unfortunately we did not measured fistula flow, therefore we could not add anything regarding this relationship. However we confirm the strong reverse relationship between PAP and ejection fraction. It has been reported that PHT improved after successful kidney transplantation, as well as after short AVF compression, indicating that both ESRD and AVF contribute to its pathogenesis [5]. In our patients those treated with HD had higher frequency of PHT than those on PD. Moreover factors associated to PHT in subjects treated with HD and PD seems to be different, probably reflecting a different degree of damage of the cardiovascular system during the history of the renal replacement treatment. To the best of our knowledge this is the first study suggesting that PHT interpretation needs to be individualized based on renal replacement therapy, suggestion reinforced by the higher interdialytic weight gain in patients with PHT than in those with normal PAP and the positive relationship between PAP and diastolic left ventricular volume. In agreement with our finding Issa el al. [10] reported that time on dialysis was the strongest correlate of an elevated right ventricular systolic pressure. The same authors stated that right ventricular systolic pressure greater than 50 mmHg was associated with significant reduced posttransplant survival [10]. On the other hand Nakhoul et al. [5] demonstrated that reduced nitric oxide production could increase PAP, PHT among HD patients who underwent successful kidney transplantation reversed, even if their AVF remained patent.

Other risk factors for PHT have been identified. Harp et al. [11] in a retrospective study suggested that age was the only risk factor, since each year of age increased the odds of having PHT by 3%. Hyperparathyroidism, by causing precipitation of calcium in many tissues, could play a role in the development of PHT secondary to pulmonary artery calcifications. This notion is supported by an experimental study in a dog model of ESRD [12]: animals with increased PTH activity and lung calcium content had higher PAP values than the dogs which underwent parathyroidectomy, thus suggesting a link between PAP and hyperparathyroidism. On the contrary Amin et al. [13] did not confirm these findings in a group of ESRD on regular HD. In our patients age, calcium, phosphate, PTH concentrations and history of parathyroidectomy revealed no difference between those with and without PHT. In a recent study Havlucu et al. [14] 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.

Kumbar et al. [15] reported, in 36 PD patients, that those with PHT had lower ejection fraction, higher prevalence of global hypokinesia and dilated left ventricular chamber than patients without PHT. In the same way our findings indicate that low cardiac performance is related to PHT in PD subjects. Moreover in agreement with Yigla et al. [2] we found a higher prevalence of valvular damage in subjects with PHT, however the difference was statistically significant only for aortic incompetence in the PD group.

The relationship between PHT and diastolic BP should be interpreted in the same way, considering low diastolic BP as an indirect index of arterial stiffness. PHT was more frequent in HD than in PD, however this could be a bias due to the fact that in the patients referred to our hospital, PD subjects are usually healthier subjects than HD ones. The latter are older than the former, and the presence of AVF in HD but not in PD patients was bound to determine different (and worse) hemodynamic conditions.

In conclusion our cross-sectional and retrospective study confirms that PHT is a frequent condition in the uraemic population, especially in aged patients with poor cardiovascular conditions. Hence, PHT could complicate the clinical picture of dialysis patients. On the other hand, our findings indicate that PAP evaluation could be a useful parameter for cardiovascular risk stratification of uraemic patients that needs to be interpreted based on patient history.

## Competing Interests

The authors declare that they have no competing interests. The authors did not get any financial support. The study has been conducted according to the Declaration of Helsinki.

## Authors' Contributions

Fabio Fabbian, Stefano Cantelli, Christian Molino, Marco Pala, Carlo Longhini, Francesco Portaluppi, performed the clinical work, acquired, analyzed and interpreted the data. Fabio Fabbian and Francesco Portaluppi drafted the manuscript Christian Molino and Carlo Longhini performed the investigations Stefano Cantelli and Marco Pala collected the data. Every author reviewed and approved the manuscript that it is not under consideration for publication elsewhere in a similar form, in any language.

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