

## ORIGINAL ARTICLE

# Pulmonary Hypertension in Patients with End Stage Renal Disease on Maintenance Hemodialysis-A Cross-sectional Study

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## Abstract

**Background:** Pulmonary Hypertension (PH) in End Stage Renal Disease (ESRD) on Maintenance Hemodialysis (HD) portends a poor outcome in patients undergoing dialysis.

**Methods:** 50 patients with ESRD undergoing regular hemodialysis for at least 3 months were included. Biochemical parameters- hemoglobin, urea, creatinine, albumin, calcium, phosphorus and PTH assessed post dialysis. All patients underwent 2D echocardiography one hour after dialysis to avoid overestimation of pulmonary artery pressures. Measurement of various parameters was carried out including right atrial and ventricular dimensions, tricuspid annular plane systolic excursion, flow across tricuspid and pulmonary valves and tissue doppler imaging of the annular plane. PH was defined as mean right ventricular systolic pressure  $\geq 25$  mmHg. Variables were compared between two groups- subjects with PH and Non-PH.

**Results:** Seventeen patients were detected to have PH. All baseline biochemical parameters did not show significant difference between two groups. On ECHO, right atrial and ventricular enlargement and pulmonary vascular resistance were significantly higher in PH group. LA vol index greater than 34ml/m<sup>2</sup> was detected in 94.1% patients with PH as opposed to 51.5% in non PH. LVEDP was detected to be significantly higher in PH compared to Non PH ( $p=0.001$ ; 94.1% vs 39.4%). Mean values of ejection fractions were also significantly different.

**Conclusion:** This study suggests that up to one third of ESRD patients on HD develop PH. Echocardiography findings reveal a significant association between raised LVEDP and increased pulmonary artery pressures. Thus, volume overload and diastolic dysfunction (heart failure with preserved ejection fraction) appear to be the main contributors to development of PH.

## Introduction

Pulmonary hypertension (PH) is characterized by raised pulmonary artery pressure which can eventually lead to right ventricular dysfunction and failure. PH in patients with chronic kidney disease (CKD) has previously been attributed to co-existing conditions such as left heart disease, sleep apnea etc. but it has been recently identified to occur as a complication of CKD itself. Estimates of pulmonary hypertension in population with CKD are 30-50%.<sup>1</sup> Development of PH due to CKD per se most likely involves interaction between multiple alterations in cardiovascular physiology that occur

such as increased peripheral vascular resistance and increased cardiac output (due to arteriovenous fistula).<sup>1</sup> Hormonal and metabolic derangements in CKD can alter endothelial function leading to imbalance in the vasodilators and vasoconstrictors affecting tone of pulmonary vasculature.<sup>2,3</sup> Development of pulmonary hypertension has been found to be an independent predictor of increased mortality and poor outcome in patients undergoing dialysis and renal transplant.<sup>1</sup>

Arteriovenous fistulas has been commonly implicated in the development of PH in CKD patients on hemodialysis as it increases cardiac output and pulmonary circulation flow.<sup>1,4</sup> State of chronic volume overload often existing in CKD patients undergoing dialysis as well as development of diastolic dysfunction have been found to contribute to PH, as they reflect increased pressures upon the pulmonary vasculature.<sup>5</sup> In a study by Agarwal et al, use of vitamin D activators was associated with lesser occurrence of PH<sup>6</sup>. Other associations found in various studies with development of PH in ESRD patients have been greater dialysis vintage,<sup>7</sup> lower hemoglobin<sup>4</sup> and smoking.<sup>8</sup> However these associations were only seen in single studies.

There are very few studies available from India which have studied the prevalence of pulmonary hypertension in CKD/ESRD patients. The paucity of data prompted us to take up the present study to find the occurrence and determinants of PH in ESRD patients on hemodialysis. Once the magnitude of the problem i.e. PH in ESRD patients is determined and its propensity to lead to poor outcomes realized, measures to prevent its development can be instituted to achieve better long-term outcomes.

The standard test for confirmation of pulmonary hypertension is right heart catheterization,<sup>9</sup> but the present study utilized echocardiography to screen patients of ESRD on maintenance hemodialysis for presence of pulmonary hypertension because of its non-invasive nature, ease of application and repetition if required.

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**Table 1: Demographic and biochemical profile**

Variables	PH group (n=17)	Non- PH group (n=33)	p value
Age	47.2 yrs	50.79 yrs	0.921
BMI	22.11 kg/m <sup>2</sup>	23.43 kg/m <sup>2</sup>	0.64
History of Diabetes	7 (41.2%)	16 (48.5%)	0.623
History of Hypertension	15 (88.2%)	28 (84.8%)	1.00
H/o Cardiovascular Ds	4 (23.5%)	3 (9.1%)	0.210
Duration of hemodialysis	2.45 yrs	2.21 yrs	0.485
Hemoglobin (g/dl)	9.22 ± 1.42	9.45 ± 1.62	0.511
Albumin (g/dl)	3.62 ± 0.45	3.77 ± 0.52	0.33
Calcium (mg/dl)	8.90 ± 0.76	8.87 ± 0.91	0.902
Phosphorus (mg/dl)	4.62 ± 1.95	4.63 ± 1.73	0.987
PTH (pg/ml)	517.94 ± 542.47	510.82 ± 591.44	0.967
Urea (mg/dl)	81.18 ± 36.62	81.94 ± 32.23	0.981
Creatinine (mg/dl)	5.01 ± 1.77	4.89 ± 1.71	0.816

**Table 2: Echocardiography examination**

Variables	PH group (Mean±SD)	Non-PH group (Mean±SD)	p values
<b>Right heart parameters</b>			
RA pressure (mmHg)	7.65 ± 1.00	7.45 ± 1.17	0.567
Right atrial volume index (ml/m <sup>2</sup> )	38.8 ± 7.60	22.8 ± 3.77	<0.001
RV base diameter (cm)	4.08 ± 0.41	2.96 ± 0.37	<0.001
Pul. Vasc. Resistance (wood units)	1.83 ± 0.49	1.32 ± 0.46	<0.001
RVSP (mmHg)	35.29 ± 6.24	15.37 ± 5.67	<0.001
TAPSE (mm)	1.6 ± 0.5	1.9 ± 0.6	0.113
<b>Left heart parameters</b>			
PCWP mean (mmHg)	12.28 ± 5.2	9.71 ± 3.1	0.035
LA volume index (ml/m <sup>2</sup> )	48.5 ± 13.6	38.6 ± 19.1	0.064
LV mass index (ml/m <sup>2</sup> )	169.59 ± 46.80	148 ± 52.36	0.159

## Material and Methods

The study was conducted at a tertiary care hospital in North India. The study was approved from Institutional Ethics Committee. Fifty consecutive patients undergoing regular hemodialysis for at least 3 months were included in the study. Data was collected over 16 months. All patients were explained in detail about the purpose of the study

**Table 3: Ejection fraction**

Ejection fraction	PHTN+ frequency (%)	PHTN- frequency (%)	P value
<50	6 (35.3)	4 (12.1)	0.052
50 - 60	10 (58.8)	18 (54.5)	0.773
>60	1 (5.9)	11 (33.3)	0.031
Mean	(49.7)	(57.8)	0.018

and an informed consent was taken. Patient's details were incorporated into a proforma. Biochemical parameters were assessed via blood samples drawn after hemodialysis session, including hemoglobin, blood urea, serum creatinine, albumin, calcium, phosphorus and PTH. All patients then underwent 2D Doppler echocardiography one hour after the dialysis to avoid overestimation of pulmonary artery pressures due to fluid overload.<sup>1</sup> Pulmonary hypertension was considered as a mean right ventricular systolic pressure (RVSP) greater than 25 mmHg. Mean RVSP was preferred as it has been found to correlate with invasively measured pulmonary artery pressures greater than peak RVSP.<sup>1,10</sup> Echocardiographic assessment was done using the Phillips HD 15 machine, 2D M mode CW/PW/Tissue doppler techniques were used in assessment of cardiac structure and hemodynamics by an experienced echocardiologist, as per guideline of American Society of Echocardiography. Standard echocardiography techniques were applied in assessment of cardiac chamber structure and function.<sup>11,12</sup>

Various parameters were measured including right atrial and ventricular dimensions, TAPSE (tricuspid annular plane systolic excursion), flow across tricuspid and pulmonary valves with continuous wave Doppler and TDI (tissue doppler imaging of the annular plane). PH was calculated by adding estimated right atrial pressure (RAP) to tricuspid regurgitant (TR) jet velocity. To get a better estimate of right atrial pressure, inferior vena cava collapsibility was used. The TR jet peak was utilized to obtain RVSP according to Bernoulli's equation:  $4 \times (\text{peak tricuspid regurgitant jet velocity})^2 + \text{estimated right atrial pressure}$ . Mean RVSP was calculated by planimetry TR jet envelop obtained by Doppler. Mean RAP was added to it to give true mean PAP.

Statistical testing was conducted with SPSS v 17.0. The comparison of normally distributed continuous

variables between the groups was performed using Student's t test. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. For all statistical tests, a p- value less than 0.05 was taken to indicate a statistically significant difference.

## Results

Fifty patients (25 males) were enrolled in the study. Seventeen patients were detected to have pulmonary hypertension. Most of the patients enrolled in the study were in the age group of 51-60 yrs (28%). Mean values of all the biochemical parameters under study did not show any significant differing factor in the two populations (PH and Non- PH group) (Table 1). One patient in the non-pulmonary hypertension group had an AV graft as vascular access, all other patients underwent dialysis via AV fistulas.

### Echocardiography examination

On echocardiography, right atrial volume index, right ventricular base diameter and pulmonary vascular resistance were significantly higher in patients with pulmonary hypertension. Mean PCWP was significantly higher in the PH group. Mean LA volume and LV mass indices were not significantly different in both groups (Table 2). However LA vol index greater than 34ml/m<sup>2</sup> was detected in 16 out of 17 patients with PH (94.1%) as opposed to 17 patients out of 33 in the non-PH group (51.5%). This difference was found to be statistically significant (p value- 0.004). Despite similar albeit raised LV mass indices in both the groups, left ventricular end diastolic pressure was detected to be high in 94.1% patients in PH group. Whereas it was detected as high in only 39.4% patients in non-PH group. This difference was found to be statistically significant (p value- 0.001). Mean values of ejection fractions were significantly different in both the groups (Table 3), being 49.7% in patients with pulmonary hypertension and 57.8% in patients without pulmonary hypertension (p value- 0.018).

## Discussion

The paucity of Indian data prompted us to take up the present study to find the occurrence and determinants of PH

in ESRD patients on hemodialysis. In the study seventeen patients, constituting one third of the study population were found to have raised pulmonary artery pressures as measured by mean right ventricular systolic pressure (RVSP) of  $\geq 25$  mmHg assessed by echocardiography. The mean of (mean) RVSP in this subpopulation was higher than in the non-PH population. In different studies the prevalence of PH has been found to vary from 30-50%<sup>1</sup>; utilization of different definitions for PH as per ECHO and different timings of echocardiograms with relation to hemodialysis have probably lead to obtaining variable prevalence estimates. No significant association was detected between pulmonary hypertension and age, gender, BMI, history of comorbidities such as diabetes and hypertension and duration of hemodialysis.

Lower hemoglobin levels have been associated with PH in studies as done by Yigla et al in Israel<sup>4</sup>, Zhilian et al in China<sup>13</sup> and Patel et al in Chennai.<sup>14</sup> This however was not detected in our study, no significant association was also seen with calcium, phosphorous or PTH levels.

Assessment of cardiac function on echocardiography revealed a significant difference in right atrial volumes and right ventricular base diameters in both the groups. Chamber dilation is expected in patients with chronic pulmonary hypertension as resistance to outflow would cause initially myocardial hypertrophy followed by chamber enlargement to increase preload and maintain right ventricular output by Starlings law. This at a later stage may be followed by decompensation, development of rising filling pressures, annular dilation and tricuspid regurgitation which may result in right heart failure.<sup>15</sup> Tricuspid annular systolic plane excursion (TAPSE), which is a marker of right ventricular function, did not show a statistically significant difference in both the groups. Reduced right ventricular function develops with increasing pulmonary artery pressures, however this is a time dependent development and thus was not seen with all patients of PH in this study population.<sup>16</sup> Emerging techniques such as strain imaging are able to identify right ventricular dysfunction at an earlier stage<sup>17</sup>, this was however not

utilized in our study.

Rise in pulmonary vascular resistance was also seen with higher right ventricular systolic pressures. This modality which is obtained by conventional doppler techniques can be used in assessing pulmonary artery pressures as well. In situations wherein right ventricular systolic function decreases which do not lead to rise in pulmonary artery pressures despite occurrence of PH, PVR is a useful marker.<sup>17,18</sup> It is also useful in distinguishing raised pulmonary artery pressures occurring from increased vascular flow or from raised vascular resistance.<sup>12</sup>

PCWP were significantly different in both the populations. The results were consistent with study by Ramsabhu et al that PCWP was found to be significantly raised in patients with PH and was detected to be a major contributor to its development.<sup>19</sup> This finding may arise in patients due to left heart systolic or diastolic dysfunction or from volume overload which is commonly seen in patients of chronic kidney disease on hemodialysis.

Left atrial volume index was also significantly raised in the population with PH as majority of patients had a value  $\geq 34$  ml/m<sup>2</sup> as compared to non-PH group. In the study by Agarwal et al,<sup>6</sup> left atrial diameter was also found to be significantly associated with PH. Left ventricular end diastolic pressures were however significantly raised in patients with PH than in the non-PH group. This factor may arise from chronic volume overload or LV diastolic dysfunction.

LVEF in both the groups were significantly different. In the study done by Yigla et al,<sup>4</sup> ejection fraction was found to be significantly higher in the population with PH. In the study by Fabbian et al, a significant negative association was revealed between ejection fractions and PH.<sup>20</sup> In the study by Ramasabhu et al, mean ejection fraction values were also found to be lower with rise in tricuspid regurgitant jet (pulmonary hypertension), however this was not found to statistically significant<sup>19</sup>. Even though the values of ejection fractions are significantly different in both the groups in this study, 49.7% signifies a largely maintained left ventricular function in the population with PH. Left ventricular mass index

is increased in both groups but LV end diastolic pressure is raised in the group with PH only, since ejection fraction is largely maintained in this group, therefore diastolic dysfunction appears to occur predominantly in these patients. Thus, the contribution of volume overload or heart failure with a preserved ejection fraction is more likely to lead to the development of pulmonary hypertension than left systolic dysfunction in this study population.

There are several limitations of the study. Small sample size of the study which did not allow for a logistic regression analysis, thus affecting the assessment of correlation of the significant associating factors. Right heart catheterization (RHC) is the gold standard invasive method for assessment of cardiac status but echocardiogram is feasible and best modality for non-invasive assessment of cardiac status was utilized in the present study. The study also excluded non-dialysis CKD patients, thus a comparison could not be made. Assessment of Kt/v would have added value to the study. However present study does add value to existing knowledge, as it provides data in an Indian population, which so far has not been much studied.

## Conclusion

Among the various complications that may arise from the end stage renal disease state, development of pulmonary hypertension portends a high cardiovascular risk. Thus, it should be actively sought in patients of chronic kidney disease. Optimization of volume status and maintenance of dry weight as much as possible should be encouraged, as it did emerge as a significant factor in the present study. Further studies of structural and functional changes in the heart, especially utilizing emerging techniques such as strain imaging should be done. Identification of cardiac abnormalities in the subclinical state and early institution of therapy may help prevent backstream complications like pulmonary hypertension from developing.

## References

1. Sise ME, Courtwright AM, Channick RN. Pulmonary hypertension in patients with chronic and end-stage kidney disease. *Kidney Int* 2013; 84:682-692.
2. McLaughlin VV, McGoon MD. Pulmonary Arterial Hypertension. *Circulation* 2006; 114:1417-31.

3. Schermuly RT, Ghofrani HA, Wilkins MR, Grimminger F. Mechanisms of disease: pulmonary arterial hypertension. *Nat Rev Cardiol* 2011; 8:443–455.
4. Yigla M, Nakhoul F, Sabag A, Tov N, Gorevich B, Abassi Z et al. Pulmonary Hypertension in Patients With End-Stage Renal Disease. *Chest* 2003; 123:1577–82.
5. Turakhia MP, Schiller NB, Whooley M. Prognostic Significance of Increased Left Ventricular Mass Index to Mortality and Sudden Death in Patients with Stable Coronary Heart Disease (From the Heart & Soul Study). *Am J Cardiol* 2008; 102:1131–1135.
6. Agarwal R. Prevalence, determinants and prognosis of pulmonary hypertension among hemodialysis patients. *Nephrol Dial Transplant* 2012; 27:3908–14.
7. Issa N, Krowka MJ, Griffin MD, Hickson LJ, Stegall MD, Cosio FG. Pulmonary hypertension is associated with reduced patient survival after kidney transplantation. *Transplantation* 2008; 86:1384–1388.
8. Fabbian F, Cantelli S, Molino C et al. Pulmonary hypertension in dialysis patients: a cross-sectional Italian study. *Int J Nephrol* 2011; doi:10.4061/2011/283475.
9. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera AJ et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2009; 30:2493–2537.
10. Er F, Ederer S, Nia AM, Caglayan E, Dahlem KM, Semmo N et al. Accuracy of Doppler- Echocardiographic Mean Pulmonary Artery Pressure for Diagnosis of Pulmonary Hypertension. *PLoS ONE* 2010; 5:e15670. doi:10.1371/journal.pone.0015670
11. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23:685–713.
12. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009; 22:107–33.
13. Li Z, Liang X, Liu S, Ye Z, Chen Y, Wang W et al. Pulmonary Hypertension: Epidemiology in Different CKD Stages and Its Association with Cardiovascular Morbidity. *PLoS ONE* 9(12): e114392. doi:10.1371/journal.pone.0114392
14. Patel P, Abraham G, Pratap B, Ramalakshmi R, Mathew M, Jeevan JM. Clinical and biochemical parameters in chronic kidney disease with pulmonary hypertension. *Indian Journal of Nephrology* 2007; 17:4–6.
15. Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR. Right Ventricular Function and Failure Report of a National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. *Circulation* 2006; 114:1883–1891.
16. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R. Independent and Additive Prognostic Value of Right Ventricular Systolic Function and Pulmonary Artery Pressure in Patients With Chronic Heart Failure. *J Am Coll Cardiol* 2001; 37:183–8.
17. Mathai S, Hassoun P. The Role of Echocardiography in the Diagnosis and Assessment of Pulmonary Hypertension. *Advances in PH Journal* 2008; 7.
18. Bossone E, D'Andrea A, D'Alto M, Citro R, Argiento P, Ferrara F, et al. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. *J Am Soc Echocardiogr* 2013; 26:1–14.
19. Ramasubbu K, Deswal A, Herdejürgen C, Aguilar D, Frost AE. A prospective echocardiographic evaluation of pulmonary hypertension in chronic hemodialysis patients in the United States: prevalence and clinical significance. *Int J Gen Med* 2010; 3:279–286.
20. Fabbian F, Cantelli S, Molino C et al. Pulmonary hypertension in dialysis patients: a cross-sectional Italian study. *Int J Nephrol* 2011; doi:10.4061/2011/283475.