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# Pulmonary hypertension and right ventricular dysfunction in hemodialysis patients

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**Abstract. – OBJECTIVE: Hemodialysis treatment has been revealed to increased the systolic pulmonary artery pressure (sPAP). Right ventricular dysfunction (RVD) had been demonstrated to predict mortality in chronic renal failure patients. We investigate the prevalence of pulmonary hypertension and RVD among patients and possible contributing factors for pulmonary hypertension.**

**PATIENTS AND METHODS: A cross-sectional survey consisted of 70 hemodialysis patients was performed in our hemodialysis center. By using echocardiography, an estimated systolic pulmonary artery pressure of > 35 mmHg at rest met the criterion of pulmonary hypertension. Tissue Doppler imaging (TDI) of the right ventricle was performed in all patients.**

**RESULTS: 27 out of 70 (38.57%) patients met the definition of pulmonary hypertension, while 32 out of 70 (45.71%) patients met the definition of RVD. Compared to patients without pulmonary hypertension, patients with pulmonary hypertension demonstrated higher systolic blood pressure and lower left ventricular ejection fraction (LVEF). RVD, indicated by TDI myocardial performance index (MPI), was worse impaired in patients with pulmonary hypertension. Echocardiographic findings suggested elevated MPI values of right ventricular and right ventricular wall thickness were significantly associated with sPAP. While a high level of LVEF and Kt/V values was inversely correlated with sPAP. The multivariate determinants of pulmonary hypertension were systolic blood pressure and Kt/V values.**

**CONCLUSIONS: Among hemodialysis patients, pulmonary hypertension is extraordinary common and is significantly associated with RVD. The poor control of systolic blood pressure and volume overload have played an important role in the mechanism of pulmonary hypertension in chronic uremia patients.**

*Key Words:*

Pulmonary hypertension, Right ventricular dysfunction, Hemodialysis, Arteriovenous fistula, Echocardiography.

## Introduction

Cardiovascular disease is one of the leading cause of mortality in chronic renal failure patients, accounting for 34.1% of deaths[1]. While maintenance hemodialysis treatment has been suggested in chronic uremia patients, it has become a financial burden in chronic kidney disease patients in Southeast China[2]. Hemodialysis treatment has been revealed to increased the systolic pulmonary artery pressure (sPAP). According to the recent studies[3-8], the prevalence of pulmonary hypertension in hemodialysis patients ranges from 20%-41.1%. Pulmonary hypertension was an independent predictor of all-cause and cardiovascular mortality in maintenance hemodialysis patients[9]. However, right ventricular dysfunction (RVD) on patients under dialysis has been rarely revealed.

Once the vascular access fistulation was successfully founded, the shunt determines a chronic increase in afterload which leads to right ventricular hypertrophy (RVH). Right ventricular (RV) compensatory hypertrophy reduces ventricular compliance and might display an underlying role in impairing left ventricular filling via interventricular interaction[10]. Echocardiography can detect sufficiently right ventricular abnormality, which can suggest prognosis in patients with pulmonary hypertension[11]. Our study investigates the prevalence of pulmonary hypertension and RVD in chronically uremia patients under hemodialysis and possible contributing factors for pulmonary hypertension.

## Patients and Methods

### Selection of Patients

This cross-sectional investigation was undertaken in West China Hospital of Sichuan University Blood Purification Center, Chengdu, China, from September 2011 until June 2013. The study popula-

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tion consisted of 70 ESRD patients (males/females: 42/28, age 54.9 ± 12.9 years) who were maintained on long-term hemodialysis therapy via surgically created native arteriovenous access. Patients ≥ 18 years who had been on maintenance therapy for at least 3 months and were receiving hemodialysis sessions 3 times per week, were enrolled. Each sessions lasted for 4h and used bicarbonate-buffered dialysate. All of these patients were used radial arteriovenous fistula. 48 patients were exclude due to comorbid conditions with a high probability of secondary pulmonary hypertension (sever valvular heart disease [n = 11], congenital left-right shunts [n = 3], a history of coronary artery stent installation [n=5 ], connective tissue disorders [n = 4], pulmonary thromboembolic disease [n = 5], chronic cor pulmonale [n = 7], chronic obstructive pulmonary disease [n = 13]). 5 patients had renal transplantation and 3 patients had atrial fibrillation were also not enrolled. All patients signed an informed consent before entering the study. Our study has been approved by West China Hospital Ethics Committee.

### Clinical and Laboratory Investigations

Each patient's general data (age, sex, systolic blood pressure, diastolic blood pressure, medication used, etiology of renal disease) and data regarding the hemodialysis (dialytic age, interdialytic weight gain, Kt/V values) were recorded. Kt/V values were calculated by Daugirdas second generation equation: $Kt/V_{sp} = -In(R-0.08\times t) + [(4-3.5\times R) \times UF/W]$, where *t* was the session length in hours and R was the ratio of postdialysis to the predialysis plasma urea nitrogen concentrations. UF is short for ultrafiltrate volume in liters. W is the postdiamysis weight in kilograms[12]. Laboratory investigations (hemoglobin, hematocrit, albumin, serum calcium, phosphorus, parathyroid hormone) were also determined. All the laboratory data were done in the same week when the patient underwent Doppler echocardiography.

### Echocardiography

All enrolled patients underwent Doppler echocardiography within 1-2 hours after completion of the hemodialysis to avoid volume overload which may lead to overestimated of sPAP. Each patient were examined by an experienced echocardiographist. All echocardiography parameters were measured by a Philips (Eindhoven, The Netherlands) iE-33 ultrasound machine. The following measurements were taken on two-Dimensional and M-mode echocardiography: diameter of left atria (LA), diameter of left ventricular (LV), diameter of right atria (RA), diameter of RV, thickness of interventricular septum (IVS) and thickness of left ventricular posterior wall (LVPW)[13]. Ejection fraction of the left ventricular was calculated using the modified Simpson method in the 4-chamber view. The tricuspid systolic jet (TR) was measured by from the 4-chamber view with the continues-wave Doppler probe. In the presence of tricuspid valve regurgitation, systolic pulmonary artery pressure was calculated using the simplified Bernoulli equation: $sPAP = 4*(TR)^2$ + right artrial pressure. Right atrium pressure was estimated from inferior vena cava (IVC) and its collapsibility. Pulmonary hypertension is defined as an increased of mean pulmonary artery pressure above 25 mmHg at rest in the setting of normal or reduced cardiac output and normal pulmonary capillary pressure.However, according to the echocardiographic criteria, pulmonary hypertension is defined as sPAP > 35 mmHg at rest[14].

Early (E) and late (A) right ventricular inflow velocities were measured with pulse-wave Doppler by placing the sample volume in between the tips of the tricuspid valve in the apical 4-chamber window. S' (systolic myocardial velocity), E' (protodiastolic myocardial velocity) and A' (late peak diastolic myocardial velocity) of the right ventricular were recorded by tissue Doppler imaging (TDI). The deceleration time (DT-E), ejection time (ET), isovolumic relaxation time (IVRT) and isovolumic contraction (IVCT) were also measured. Calculation of right ventricular myocardial performance index (MPI) by tissue Doppler imaging is defined as the ratio of isovolumic time divided by (IVRT + IVCT)/ET. TDI of MPI value is reproducible and relatively independent of preload. The upper reference limit for the right-sided TDI of MPI value is 0.55[15]. Tricuspid annular plane systolic excursion (TAPSE), indices of right ventricular systolic function, was acquired by placing an M-mode cursor through tricuspid annulus. TAPSE is a method to measure the amount of longitudinal motion of the RV annular segment at peak systole. It is inferred that the greater the descent of the base in systole is associated with better RV systolic function[14]. The four chambers were measured through apical 4-chamber view at the same time. RV wall thickness was measured at end-diastole by M-mode from the subcostal window, at the level of the tip of the anterior tricuspid leaflet or left parasternal windows. Right ventricular hypertrophy was defined as RV wall thickness ≥ 5 mm[16].

The vascular access was acquired soon after in the longitudinal and transverse planes from the arterial anastomosis through the entire access by means of ultrasonic Doppler (Philips iE-33 ultrasound machine). Vascular blood flow was calculated by multiplying the time-averaged velocity (TAV) by the cross-sectional area of the access[17]. The calculations of vascular blood flow is $Qa = TAV \times \pi r^2 \times 60$. Here, r is the radius of the arterial anastomosis.

### Statistical Analysis

Values are expressed as means ± standard deviation and as a percentage for categorical parameters. Clinical variables were compared between patients with and without pulmonary hypertension. Differences between continuous variables of the two subgroups were compared with Student's *t*-test and Mann-Witney-U test, as applicable. Chi-square test was used to evaluate the categorical parameters between the groups. Two-tailed bivariate correlations were estimated by the Pearson's coefficient. Multivariate regression analysis was performed to determine the relationship between pulmonary hypertension and other covariates (demographic, clinical or hemodynamic). Those convariates were required to have a *p*-value of < 0.2 to enter the stepwise forward selection and a p-value of < 0.05 to remain in the final model. All analyses were conducted using standard statistical software (IBM, SPSS 20.0 New York, NY, USA). All *p* values < 0.05 were considered to be statistically significant.

## Results

### Baseline Characteristics

Data from the 27 patients with pulmonary hypertension were compared with those of the 43 patients without pulmonary hypertension (Table I). Groups did not show significant differences regarding the age, gender, body mass index (BMI), heart rates and diastolic blood pressure. However, the systolic blood pressure was significant higher in pulmonary hypertension patients as compared with those without pulmonary hypertension (Table I). The common etiologies of renal failure were hypertension, diabetes mellitus, glomerulonephritis. The incidence of antihypertensive medications were distributed in similar proportions (Table I). The mean duration of dialysis as well as the interdialytic weight gain in patients demonstrated no significant differences between the two subgroups.Interestingly, the Kt/V values was lower in patients with pulmonary hypertension (Table I).

**Table I.** Demographic and Clinical data of patients (n=number of patients).

| Variable | sPAP ≤35 mmHg (n: 43) | sPAP > 35 mmHg (n: 27) | *p* value |
|---|---|---|---|
| Age (years) | 55.49 ± 11.74 | 55.46 ± 14.95 | 0.765 |
| Gender, male/female ratio | 1.39 | 1.70 | 0.488 |
| BMI (kg/m$^2$) | 23.20 ± 3.37 | 21.70 ± 2.63 | 0.059 |
| Heart rate (beats/min) | 77.47 ± 9.35 | 72.19 ± 15.69 | 0.084 |
| Systolic blood pressure (mmHg) | 138.72 ± 15.01 | 152.08 ± 16.11 | 0.001 |
| Diastolic blood pressure (mmHg) | 80.44 ± 10.27 | 83.16 ± 11.53 | 0.313 |
| Etiology of renal failure | | | 0.549 |
| • Hypertension (%) | 7 | 8 | ns |
| • Diabetes mellitus (%) | 11.6 | 15.4 | ns |
| • Glomerulonephritis (%) | 48.8 | 57.7 | ns |
| • Others (%) | 25.6 | 8 | ns |
| • Unknown (%) | 7 | 10.9 | ns |
| Antihypertension therapy | | | ns |
| • ACE-inhibitors (%) | 7 | 12 | 0.833 |
| • ARBs (%) | 32 | 46 | 0.259 |
| • β-Blockers (%) | 42 | 69 | 0.057 |
| • CCB (%) | 90 | 81 | 0.413 |
| • α-Blockers (%) | 28 | 38 | 0.869 |
| Dialytic age (months) | 40.16 ± 38.89 | 31.25 ± 16.67 | 0.193 |
| Interdialytic weight gain (kg) | 2.18 ± 0.71 | 2.10 ± 0.72 | 0.681 |
| Kt/V value | 1.85 ± 0.90 | 1.31 ± 0.30 | 0.001 |

Footnote: ARBs, angiotensin receptor blockers; CCB, calcium channel blockers. 1 mmHg = 0.1333 kPa.

**Table II.** Laboratory characteristics of patients (n=number of patients).

| Variable | sPAP ≤ 35 mmHg (n:43) | sPAP > 35 mmHg (n:27) | p value |
|---|---|---|---|
| Hemoglobin (g/L) | 102.24 ± 16.55 | 93.19 ± 14.27 | 0.024 |
| Hematocrit (%) | 0.32 ± 0.05 | 0.29 ± 0.05 | 0.020 |
| Albumin (g/L) | 42.60 ± 3.33 | 41.98 ± 3.99 | 0.491 |
| Calcium (mmol/l) | 2.33 ± 0.31 | 2.29 ± 0.24 | 0.651 |
| Phosphate (mmo/l) | 1.85 ± 0.55 | 1.65 ± 0.46 | 0.139 |
| PTH (pg/ml) | 20.99 ± 17.89 | 21.44 ± 18.35 | 0.854 |

### Indices of Laboratory Investigations

The levels of hemoglobin and hematocrit were significantly lower in patients with pulmonary hypertension. Although the albumin seemed to be lower in patients with pulmonary hypertension, the two subgroups did not differ significantly different. Other variables, such as serum calcium, phosphorus and parathyroid hormone (PTH) did not differ significantly between the examined subgroups (Table II).

### Indices of Right Ventricular Function

Patients on hemodialysis with pulmonary hypertension presented higher left and right ventricular diameters (Table III). In particularly, sPAP and RV wall thickness were significantly higher in patients with pulmonary hypertension compared with those without pulmonary hypertension (44.15 ± 7.80 vs 25.95 ± 5.81 mmHg, $p < 0.001$; 4.56 ± 0.72 vs 4.17 ± 0.51 mm, $p = 0.012$, respectively) (Table III). Moreover, 33.33% of patients were re-

**Table III.** Echocardiographic parameters of patients (n=number of patients).

| Variable | sPAP ≤ 35 mmHg (n:43) | sPAP > 35 mmHg (n:27) | p value |
|---|---|---|---|
| sPAP (mmHg) | 25.95 ± 5.81 | 44.15 ± 7.80 | < 0.001 |
| LA diameter (mm) | 37.09 ± 5.22 | 42.12 ± 3.94 | < 0.001 |
| LV diameter (mm) | 46.47 ± 4.57 | 52.80 ± 6.16 | < 0.001 |
| RA diameter (mm) | 41.44 ± 7.11 | 46.88 ± 7.14 | 0.003 |
| RV diameter (mm) | 21.19 ± 2.14 | 23.85 ± 4.67 | 0.010 |
| IVS (mm) | 11.99 ± 1.88 | 12.81 ± 1.90 | 0.085 |
| LVPW (mm) | 10.51 ± 1.65 | 11.31 ± 1.80 | 0.066 |
| RV wall thickness (mm) | 4.17 ± 0.51 | 4.56 ± 0.72 | 0.012 |
| Presence of RV hypertrophy (%) | 9.30 % | 33.33% | < 0.001 |
| Pulse Doppler imaging | | | |
| Tricuspid E (cm/s) | 59.52 ± 12.39 | 56.75 ± 11.74 | 0.296 |
| Tricuspid A (cm/s) | 52.40 ± 12.39 | 48.32 ± 9.54 | 0.154 |
| E/A ratio | 1.19 ± 0.30 | 1.22 ± 0.36 | 0.653 |
| DT-E (ms) | 114.21 ± 27.89 | 114.85 ± 29.31 | 0.928 |
| Tissue Doppler imaging | | | |
| Tricuspid E' (cm/s) | 9.80 ± 2.53 | 11.47 ± 2.03 | 0.006 |
| Tricuspid A' (cm/s) | 13.97 ± 3.39 | 15.56 ± 4.75 | 0.145 |
| Tricuspid annulus systolic peak velocity S' (cm/s) | 13.16 ± 2.13 | 14.08 ± 1.71 | 0.068 |
| E'/A' ratio | 0.74 ± 0.29 | 0.82 ± 0.34 | 0.348 |
| TAPSE (mm) | 23.61 ± 2.95 | 22.11 ± 2.66 | 0.033 |
| ET (ms) | 254.70 ± 27.29 | 264.85 ± 27.42 | 0.140 |
| IVRT (ms) | 60.2 ± 15.11 | 76.12 ± 12.41 | < 0.001 |
| IVCT (ms) | 70.51 ± 10.99 | 73.88 ± 10.52 | 0.214 |
| MPI value | 0.52 ± 0.09 | 0.57 ± 0.06 | 0.010 |
| LVEF (%) | 67.84 ± 7.52 | 60.19 ± 10.81 | 0.039 |

vealed to developed to RVH in patients with pulmonary hypertension. While only 9.30% patients without pulmonary hypertension resulted in RVH.

Compared with the patients without pulmonary hypertension, patients with pulmonary hypertension showed a prolonged IVRT but lower TAPSE (Table III). MPI values, echocardiography parameters of right ventricular systolic and diastolic function,was significantly higher in patients with pulmonary hypertension ($p = 0.033$ and $p = 0.010$ respectively) (Table III). It indicated that right ventricular function was impaired in patients with pulmonary hypertension than those without pulmonary hypertension.

### Indices of Vascular Access

Vascular access parameters including the diameter of the arteriovenous fistula and the vascular access flow (Qb) were measured by ultrasonic Doppler at the same time. Patients with pulmonary hypertension had higher Qb compared with patients with normal sPAP (1004.25 ± 179.83 ml/min vs. 996.80 ± 220.03 ml/min). However, the difference was no statistically significant ($p = 0.887$).

### Risk of Pulmonary Hypertension in Hemodialysis Patients

A significantly positive correlation was noted between sPAP and those three parameters as RV wall thickness (r = 0.460, $p < 0.001$), MPI values (r = 0283, $p = 0.019$) and systolic blood pressure (r = 0.279, $p = 0.020$). On the contrary, sPAP inversely correlated with left ventricular ejection fraction (LVEF) (r = -0.27, $p = 0.025$), hemoglobin (r = -0.337, $p = 0.005$) and Kt/V values (r = -0.330, $p = 0.006$). A further comparison between the two uremic subgroups revealed that LVEF was significantly lower in patients with pulmonary hypertension than those without pulmonary hypertension (Table III). Logistic regression analysis adjusted for the same confounding factors such as age, gender, BMI and HR. The multivariate determinants of pulmonary hypertension were systolic blood pressure (regression coefficient b: 0. 050,odds ratio 1.051 per mmHg, $p = 0.011$) and Kt/V values (regression coefficient b: -1.394, odds ratio 0.248, $p = 0.044$).

## Discussion

The study confirmed that uremic patients on chronic dialysis treatment showed a high prevalence of pulmonary hypertension which had been reported in the previous studies[18,19]. The mechanisms of pulmonary hypertension mainly derived from elevated pulmonary blood flow and increased pulmonary vascular resistance. Pulmoanry artery pressure may be increased by high cardiac output due to the arteriovenous access, further worsened by fluid overload in hemodialysis patients. Pressure-induced mediator regulation may represent an early event in the development of secondary pulmonary hypertension in chronic renal failure patients. Prolonged hypertension may effect pulmonary circulation. A recent research confirmed that endothelial dysfunction were associated with increased vasoconstrictors like ehdothelin-1 and decreased vasodilators such as NO[20]. Worsen, chronic renal failure patients displayed metabolic and hormonal derangements which may result in pulmonary arterial vasoconstriction.

A positive relationship between the sPAP and RV wall thickness was revealed. To adopting to the high pressure of pulmonary circulation, end sysytolic pressure of right ventricle increased. Chronic right ventricular pressure overload leads to functional tricuspid valve insufficiency, initiating pathological RV remodeling and results in compensatory RVH to decrease wall stress, which ultimately leading to right heart failure. It has attributed direct ventricular interaction to the septum, via the trans-septal pressure gradient[21]. This pathological physiology change was confirmed by the negative correlation between LVEF and RV wall thickness in our study.

Although researches have mainly focused their attention on left ventricular function in hemodialysis patients[22,23], insight into the role of RV function in pulmonary hypertension patients is scarce. TDI has considered as a strong diagnostic method in detecting subclinical abnormalities in cardiac function, which had been demonstrated to predict mortality[24,25]. Thus, the detection of RVD would be helpful in early detection of higher risk of developing right heart failure. Our study revealed that nearly half of hemodialysis were associated with RVD. Interestingly, MPI values was positively correlated with sPAP. The potential mechanism of this clinical feature is chronic volume overload has affect right ventricular function independently from post-load conditions[10]. Arteriovenous fistula induced volume overload lead to increased sPAP plays a crucial role in triggering RVD in maintenance hemodialysis patients.

Although the present study showed no direct relationship between access flow of AVF and sPAP, which was similar to other clinical trails[3-26].

We avoided the patients with brachial AVFs. The blood flow of AVF was confirmed to be higher in upper arm AVFs than lower AVFs[27]. Although our study demonstrated a high prevalence of pulmonary hypertension and RVD among hemodialysis patients, it provoques some criticisms. All the vascular access parameters were measured by ultrasonic Doppler in the present study, which will be less reliably than Transonic Hemodialysis Monitor HD02[28]. As peritoneal dialysis patients who were reported had pulmonary hypertension in the recent research[29], data of RVD in those patients are lacking up to now which will be a research topic in the future.

### Conflict of Interest

The Authors declare that there are no conflicts of interest.

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