Pulmonary hypertension in patients with stage 1-3 chronic kidney disease

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ABSTRACT. Pulmonary hypertension (PH) secondary to chronic kidney disease (CKD) is common, but in stages 1-3 CKD patients, it remains unclear. We sought to evaluate the prevalence of PH and elucidate the possible pathogenesis in Chinese patients with early stage kidney disease. Doppler-estimated pulmonary systolic artery pressure (PASP) was measured in 101 CKD patients with glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m² and 27 CKD patients with GFR < 60 mL/min/1.73 m². Echocardiographic parameters, plasma brain natriuretic peptide (BNP), and baseline characteristics of patients were recorded. PH was defined as a PASP ≥ 35 mmHg. PH prevalence was 23.76% (24/101) in GFR ≥ 60 mL/min/1.73 m² group and 48.15% (13/27) in GFR < 60 mL/min/1.73 m² group, P < 0.05. Mean lnBNP was 4.93 ± 1.60 pg/mL in 37 cases with PH and 2.89 ± 1.29 pg/mL in those without, P < 0.01. Left atrial diameter (LA) showed deviation between patients with (43.94 ± 5.81 mm) and without PH (37.76 ± 7.48 mm), P < 0.01. GFR declined significantly in PH group (44.10 ± 22.90 mL/min/1.73 m²) compared to non-PH group (75.59 ± 31.62 mL/min/1.73 m²), P < 0.01. lnBNP, LA and GFR were independent determinants (r = 0.651, 0.595, -0.488, P < 0.01) of PASP. PH is prevalent among stage 1-3 CKD patients in China. Doppler-estimated PASP is strongly associated with lnBNP, enlarged LA and GFR. Monitoring PASP, plasma BNP and evaluation renal function may help to detect and
prevent severe PH in CKD.

Key words: Pulmonary hypertension; Pulmonary artery pressure; Chronic kidney disease

INTRODUCTION

Pulmonary hypertension (PH) has been traditionally defined as a mean pulmonary artery pressure of at least 25 mmHg at rest, with a pulmonary capillary wedge pressure of 15 mmHg or less. Significant PH can cause deterioration of right ventricular function, precipitating hemodynamic collapse and death (Rich, 1988).

PH has been increasingly recognized in patients with chronic kidney disease (CKD), and is not simply confined to those with connective tissue and systemic diseases. PH in patients with CKD may be induced and/or aggravated by left ventricular (LV) disorders as well as the presence of risk factors typical to CKD, including volume overload, an arteriovenous fistula (Abdelwhab and Elshinnawy, 2008), sleep-disordered breathing (Sakaguchi et al., 2011), exposure to dialysis membranes (Kiykim et al., 2010), endothelial dysfunction (Zoccali, 2007), vascular calcification and stiffening, and severe anemia (Buemi et al., 2007). Preventing PH in this population is crucial, as even kidney transplantation may not reverse the high mortality associated with PH. Therefore, greater emphasis needs to be placed on CKD patients, even during early stages of the disease.

However, there is no data on the prevalence of PH in patients with stage 1-3 CKD [according to Kidney Disease Outcomes Quality Initiative (KDOQI)]. The pathogenesis of PH in this group of patients is not explained satisfactorily. Based on a retrospective analysis of 128 CKD patients, this article investigates the pulmonary artery systolic pressure (PASP) change pattern and its relationship with cardiovascular structure and function, in order to strengthen the understanding of PH and its relevant mechanisms in earlier stages of CKD.

MATERIAL AND METHODS

Material selection

Pre-dialysis patients with CKD were included during January 2008 to December 2010. The etiologies for CKD included primary glomerulonephritis (IgA nephropathy, membrane nephropathy, focal segmental glomerular sclerosis, etc.), diabetic kidney disease, and chronic ischemic renal disease. Patients with thoracic or lung disease, left-right shunt congenital heart disease, connective tissue disease, appetite inhibitive medications history (e.g., fenfluramine, dexamphetamine), erythropoietin history and HIV infection history were excluded. All patients had complete demographic data and underwent echocardiography.

Clinical and laboratory investigations

Patient data on baseline characteristics [age, gender, height, weight, body mass index (BMI), medication used] and kidney disease (etiology of renal disease) were recorded. Brain natriuretic peptide (BNP) in EDTA-anticoagulated venous blood was tested by Triage from Biosite. Glomerular filtration rate (GFR) was measured using $^{99m}$Tc-DTPA.

Doppler echocardiography was performed by one experienced operator using Vivid 7...
Pro with 3S probe with 1.5-3.6 MHz image frequency and 1.8-2 MHz Doppler frequency (General Electric Co., USA). Two-dimensional and M-mode echocardiography was performed. A tricuspid systolic jet was recorded from the parasternal or apical window with the continuous-wave Doppler probe. The PASP or systolic right ventricular pressure was calculated using the Bernoulli equation: \( \text{PASP} = 4 \times (\text{tricuspid systolic jet})^2 + 10 \text{mmHg} \) (estimated right atrial pressure) (Berger et al., 1985). PH was defined as a \( \text{PASP} \geq 35 \text{mmHg} \) (Reisner et al., 1994).

**Data analysis**

All statistical analysis were performed using the SPSS 13.0 software. Continuous variables are reported as means ± standard deviation. Non-normal distributed variables were transformed into normal style. Unpaired two tailed \( t \)-test and chi-squared test were generated between group comparison. Linear regression analysis was realized between PASP with both echocardiography data and lnBNP, leading to Pearson’s correlation coefficient. Figures performed using Microsoft Excel 2010. P values less than 0.05 were considered to be statistically significant.

**RESULTS**

There were 62 men and 66 women with a mean age of 53.39 ± 17.52 years (range 17-97). In patients with GFR ≥ 60 mL/min/1.73 m\(^2\) (mean 77.52 ± 26.95 mL/min/1.73 m\(^2\)), there were 45 men and 56 women with a mean age of 51.50 ± 16.57 years (range 17-86). In patients with GFR < 60 mL/min/1.73 m\(^2\) (mean 21.93 ± 9.36 mL/min/1.73 m\(^2\)), there were 17 men and 10 women with a mean age of 61.41 ± 19.06 years (range 24-97). The etiologies of kidney injury were primary glomerulonephritis (IgA nephropathy, membrane nephropathy, and focal segmental glomerular sclerosis), diabetic kidney disease, and chronic ischemic renal disease. The mean PASP was 32.37 ± 8.55 mmHg (range 0-62). PH incidence was 28.91% (37/128) overall, with 23.76% (24/101) in GFR ≥ 60 mL/min/1.73 m\(^2\) group and 48.15% (13/27) in GFR < 60 mL/min/1.73 m\(^2\) group. Demographic values were not significantly different between GFR ≥ 60 mL/min/1.73 m\(^2\) patients and GFR < 60 mL/min/1.73 m\(^2\) patients. There was no significant difference between GFR ≥ 60 mL/min/1.73 m\(^2\) and GFR < 60 mL/min/1.73 m\(^2\) groups according to echocardiography findings [LV end-diastolic (LVDd), LV end-systolic (LVDs), interventricular septum thickness (IVST), LV post wall (LVPW), LV ejection fraction (LVEF), and LV mass index (LVMI)], mean artery blood pressure (MAP), and BMI. The mean values of lnBNP and left atrial diameter (LA) showed obvious differences between patients with GFR ≥ 60 mL/min/1.73 m\(^2\) and patients with GFR < 60 mL/min/1.73 m\(^2\). The former valued 3.20 ± 1.52 pg/mL and 39.54 ± 5.81 mm, and the latter, 4.60 ± 1.75 pg/mL and 42.19 ± 5.96 mm (Table 1).

The mean PASP in 37 patients was ≥35 mmHg, ranging from 35 to 62 mmHg. There were no differences between patients with PH and patients without PH according to gender ratio and BMI. In patients with PH, there were 23 men and 14 women with a mean age of 65.16 ± 15.39 years (range 30-97). In patients without PH, 39 men and 52 women with a mean age of 48.88 ± 16.15 years (range 17-86). GFR declined significantly in PH group patients with a mean of 44.10 ± 22.90 mL/min/1.73 m\(^2\) (range 6.70-78.50), when compared to non-PH group patients, with a mean of 75.59 ± 31.62 mL/min/1.73 m\(^2\) (range 14.70-183.00). PH group patients exhibited higher MAP of 166.15 ± 31.46 mmHg than the non-PH group, at 146.99 ± 28.53 mmHg. The mean lnBNP was 4.93 ± 1.60 pg/mL in 37 cases with PH, 2.89 ± 1.29 pg/mL.
in cases with PASP < 35 mmHg. Doppler echocardiography in the PH cases (e.g., LVDD, LVDS, IVST, LVPW, LVEF) showed significant deviation from the non-PH group. The LVMI was also significantly different between the two groups (Table 2). The PASP showed a positive correlation with patient age, lnBNP, diameters of LVDD, LVDS, IVST, LVPW, and LVMI. However, the PASP had a negative correlation with GFR and LVEF. By linear regression analysis, with PASP as dependent variable and the above factors as covariates, we found independent determinants for PASP, lnBNP, LA, and GFR. The regression equation was PASP = 3.637 + 2.536 x lnBNP + 0.622 x LA - 0.075 x GFR (F = 20.944, P < 0.001) (Table 3, Figure 1).

Table 1. Patients’ demographics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with GFR ≥ 60 mL/min</th>
<th>Patients with GFR &lt; 60 mL/min</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>101</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.50 ± 16.57</td>
<td>61.41 ± 19.06</td>
<td>0.008</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.138</td>
</tr>
<tr>
<td>Male</td>
<td>45</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>56</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>24.44 ± 4.06</td>
<td>24.02 ± 3.41</td>
<td>0.650</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>77.52 ± 26.95</td>
<td>21.93 ± 9.36</td>
<td>0.000</td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>31.31 ± 7.81</td>
<td>36.33 ± 10.10</td>
<td>0.022</td>
</tr>
<tr>
<td>PH (N, %)</td>
<td>24 (23.76)</td>
<td>13 (48.15)</td>
<td>0.013</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>149.44 ± 27.86</td>
<td>163.67 ± 36.96</td>
<td>0.049</td>
</tr>
<tr>
<td>lnBNP (pg/mL)</td>
<td>3.20 ± 1.52</td>
<td>4.60 ± 1.75</td>
<td>0.001</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>39.94 ± 5.81</td>
<td>42.19 ± 5.96</td>
<td>0.039</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>48.29 ± 3.81</td>
<td>50.42 ± 4.92</td>
<td>0.298</td>
</tr>
<tr>
<td>LVDS (mm)</td>
<td>31.59 ± 5.22</td>
<td>33.91 ± 5.32</td>
<td>0.183</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>9.53 ± 1.53</td>
<td>10.19 ± 1.80</td>
<td>0.059</td>
</tr>
<tr>
<td>LVPW (mm)</td>
<td>9.39 ± 2.30</td>
<td>9.39 ± 1.90</td>
<td>0.268</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.64 ± 0.06</td>
<td>0.62 ± 0.05</td>
<td>0.069</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>99.93 ± 30.81</td>
<td>113.09 ± 38.91</td>
<td>0.086</td>
</tr>
</tbody>
</table>

BMI = body mass index; GFR = glomerular filtration rate; PASP = pulmonary artery systolic pressure; PH = pulmonary hypertension; MAP = mean artery blood pressure; LA = left atrial diameter; LVDD = left ventricle end-diastolic diameter; LVDS = left ventricle end-systolic diameter; IVST = interventricular septum thickness; LVPW = left ventricular posterior wall thickness; LVEF = left ventricular ejection fraction; LVMI = left ventricular myocardial mass index. Results are reported as means ± standard deviation.

Table 2. Comparison of patients with and without pulmonary hypertension.

<table>
<thead>
<tr>
<th>Variables</th>
<th>PASP &lt; 35 mmHg</th>
<th>PASP ≥ 35 mmHg</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>91 (71.09)</td>
<td>37 (28.91)</td>
<td>0.000</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.88 ± 16.15</td>
<td>65.16 ± 15.39</td>
<td>0.074</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>24.74 ± 3.42</td>
<td>23.39 ± 4.92</td>
<td>0.088</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>75.59 ± 31.62</td>
<td>44.10 ± 22.90</td>
<td>0.000</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>146.99 ± 28.53</td>
<td>166.12 ± 31.46</td>
<td>0.004</td>
</tr>
<tr>
<td>lnBNP (pg/mL)</td>
<td>2.89 ± 1.29</td>
<td>4.93 ± 1.60</td>
<td>0.000</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>37.76 ± 7.48</td>
<td>43.94 ± 5.81</td>
<td>0.000</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>49.53 ± 4.57</td>
<td>53.19 ± 5.56</td>
<td>0.000</td>
</tr>
<tr>
<td>LVDS (mm)</td>
<td>31.04 ± 4.76</td>
<td>34.11 ± 5.84</td>
<td>0.003</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>9.31 ± 1.40</td>
<td>10.58 ± 1.73</td>
<td>0.000</td>
</tr>
<tr>
<td>LVPW (mm)</td>
<td>9.24 ± 2.32</td>
<td>10.17 ± 1.84</td>
<td>0.034</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.65 ± 0.06</td>
<td>0.60 ± 0.05</td>
<td>0.000</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>92.83 ± 22.46</td>
<td>127.81 ± 41.45</td>
<td>0.000</td>
</tr>
</tbody>
</table>

PASP = pulmonary artery systolic pressure; BMI = body mass index; GFR = glomerular filtration rate; PH = pulmonary hypertension; MAP = mean artery blood pressure; LA = left atrial diameter; LVDD = left ventricle end-diastolic diameter; LVDS = left ventricle end-systolic diameter; IVST = interventricular septum thickness; LVPW = left ventricular posterior wall thickness; LVEF = left ventricular ejection fraction; LVMI = left ventricular myocardial mass index. Results are reported as means ± standard deviation.
Table 3. Pulmonary artery systolic pressure risk factors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>T</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR</td>
<td>-0.488</td>
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</tr>
<tr>
<td>Age</td>
<td>0.496</td>
<td>0.000</td>
</tr>
<tr>
<td>MAP</td>
<td>0.398</td>
<td>0.000</td>
</tr>
<tr>
<td>lnBNP</td>
<td>0.651</td>
<td>0.000</td>
</tr>
<tr>
<td>LA</td>
<td>0.595</td>
<td>0.000</td>
</tr>
<tr>
<td>LVMi</td>
<td>0.404</td>
<td>0.003</td>
</tr>
<tr>
<td>LVDs</td>
<td>0.377</td>
<td>0.005</td>
</tr>
<tr>
<td>IVST</td>
<td>0.457</td>
<td>0.001</td>
</tr>
<tr>
<td>LVFW</td>
<td>0.431</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.338</td>
<td>0.011</td>
</tr>
<tr>
<td>LVMi</td>
<td>0.382</td>
<td>0.000</td>
</tr>
</tbody>
</table>

For abbreviations, see legend to Table 1.

Figure 1. Pulmonary artery systolic pressure (PASP) of 128 patients with predialysis chronic kidney disease was independently correlated with mean values of lnBNP, left atrial diameter and glomerular filtration rate (GFR) by linear regression analysis. A. Negative correlation between PASP and GFR. B. Positive correlation between left atrial (LA) diameter and PASP. C. Negative correlation between PASP and lnBNP.

DISCUSSION

PH is a clinical syndrome characterized by elevated pulmonary artery pressure and vascular resistance. Elevation of pulmonary artery pressure is often superior to clinical history and physical examination (Himelman et al., 1988; Rich, 1988). Strictly, PH is defined as a mean pulmonary artery pressure exceeding 25 mmHg at rest, or 30 mmHg during exercise by right-sided cardiac catheterization (Badesch et al., 2009). Echo-Doppler estimated PASP,
a commonly applied non-invasive measurement, plays a key role in the diagnosis, prognosis and follow-up of patients with PH. Under Doppler echocardiography studies, measurement of PASP is based on the tricuspid regurgitation jet. In the absence of pulmonary stenosis, right ventricular systolic pressure, or PASP, is estimated using a modified Bernoulli equation and is computed as 4 times the square of the maximum tricuspid regurgitation jet velocity, plus right atrial pressure (which in turn can be estimated from the vena cava diameter and degree of its inspiratory collapse) (Rudski et al., 2010). Often, a fixed estimate of right atrial pressure is added when the inferior vena cava is not evaluated during echocardiography. Varied cutoffs of PH have been adopted in studies, ranging from 25 to ≥45 mmHg (Yigla et al., 2009; Kiykim et al., 2010), which result in different conclusions about PH prevalence. Here, we adopted the PH diagnostic criteria as a PASP ≥ 35 mmHg (Buemi et al., 2007).

PH comprises a group of clinical and pathophysiological entities with similar features, but various underlying causes, including CKD (Havlucu et al., 2007; Domenici et al., 2010). The prevalence of PH ranges from 9-39% in predialysis patients with stage-5 CKD (Yigla et al., 2003; Buemi et al., 2007; Havlucu et al., 2007; Abdelwhab and Elshinnawy, 2008; Issa et al., 2008), 18.8-68.8% in hemodialysis patients, and 0-42% in individuals on peritoneal dialysis therapy (Kumbar et al., 2007; Bozbas et al., 2009; Unal et al., 2009; Casas-Aparicio et al., 2010; Kiykim et al., 2010; Fabbian et al., 2011; Agarwal, 2012; Etemadi et al., 2012). In our study, 37 of 128 (28.91%) CKD patients from China, who accepted no dialysis or renal transplantation, had Doppler-derived PASP ≥ 35 mmHg. Thus, PH incidence in predialysis CKD cases reached 28.91%, in accordance with data reported above. Given that other conditions related to PH were strictly excluded in advance, we reconfirmed that CKD led to PH. Essential Doppler measurement and careful attention should be taken to identify this PH phenomenon. Studies on PH have been performed in patients who either reached end stage of renal disease or accepted renal replacement therapy, however, few focused on patients with earlier stages of CKD. In our study, differences were uncovered between patients in GFR ≥ 60 mL/min/1.73 m² group and patients in GFR < 60 mL/min/1.73 m² group. Although PH prevalence reached 48.15% (13/27) in the GFR < 60 mL/min/1.73 m² group, the GFR ≥ 60 mL/min/1.73 m² group (with less renal injury) still has a prevalence of 23.76%, 24 of 101 CKD patients. It raises the alarm that PH exists and may be prevalent prior to a drop in the GFR to 60 mL/min/1.73 m².

We observed differences between patients with and without PH according to age, MAP, GFR, lnBNP, and echocardiography (LA, LVDD, LVDs, IVST, LVPW, LVEF, LVMI). This implies that pulmonary artery pressure is determined by a diverse set of complex factors in CKD patients.

BNP, a hormone mainly produced and released in the left ventricle as a consequence of pressure or volume load, is believed to be involved in PH. It was reported that BNP was related to PASP in primary PH (Leuchte et al., 2004), and a supplementary dose of BNP reduces PASP levels (Cargill and Lipworth, 1995). BNP is a sensitive and specific predictor of LV systolic failure (Vasan et al., 2002), a very useful tool to confirm LV diastolic dysfunction (LVEF ≥ 45-50%) (Wei et al., 2005) and is in accordance with volume overload (Kunii et al., 2003) at the same time. Plasma BNP increased with loss of renal function (Lang et al., 1992). In this study, we noticed in patients of chronic kidney disease a significant positive correlation between PASP and lnBNP. It suggests that BNP plays an important role in pulmonary hypertension secondary to kidney disease. We found that the LVMI, an indication for LV hypertrophy, increased in accordance to plasma BNP, and there was no value of LVEF (the
minimum value is 48% in our study) below 45%. Thus, volume overload, implicated in LV
disorders and in the high venous return, and LV diastolic dysfunction, an alteration found in
patients with CKD to increase pulmonary venous and arterial pressure (Tiengo et al., 2008),
may together induce PH by increasing pulmonary blood flow and adversely affecting LV
function.

In addition to BNP, the LA was the second important factor determining the PASP in-
dependently. We observed larger values of LVMI in patients with PH. LV hypertrophy causes
diastolic disorder of the left ventricle, which is then followed by an increase in LA. Then, pul-
monary circulation is pulled into a high pressure network, followed by upregulated pulmonary
venous pressure (Tiengo et al., 2008), and finally, pulmonary artery hypertension.

The decrease in kidney function may be a trigger for the development of PASP distur-
bance. GFR was negatively correlated with PASP in our study. The Doppler-estimated PASP
increased inversely to renal function. In kidney disease, a series of complications appears
eventually, such as anemia, endothelial dysfunction, LV dysfunction, and volume overload.
Severe anemia, an established cardiovascular risk factor in CKD, may extend its impact to
pulmonary circulation. Low hemoglobin levels may contribute to PH by aggravating hypoxia
triggered by concomitant conditions (Buemi et al., 2007). Endothelial dysfunction is a main
trigger of pulmonary hypertension (Giaid, 1998). This link is even close in CKD patients,
whose endothelial dysfunction is pervasive (Zoccali, 2007). The impaired capacity of the en-
dothelium to regulate vascular tone in CKD patients relies on a disturbance between vaso-
constrictors (e.g., high levels of endothelin 1) and vasodilators [reduced generation of nitric
oxide (NO)] (Giaid and Saleh, 1995; Kunii et al., 2003). ADMA, an endogenous inhibitor of
NO synthase, attains very high concentrations in patients with kidney disease (Zoccali et al.,
2001). Our continuing studies will uncover the issues of anemia, endothelin 1/NO and other
relevant conditions in early stages of CKD.

In a general population based study (Lam et al., 2009), PASP was related directly to
age and systolic pressure in patients over 45 years old, which suggests that pulmonary artery
stiffening plays a role in the development of PH. Through our study in CKD patients, the level
of PASP elevated in the same direction as aging and MAP. Therefore, pulmonary artery stiff-
ening, the aging process, and systemic blood pressure all contribute to PH. However, the influ-
ence was confined to some extent, and the efficacy faded with progression of renal disease.

Based on our observations, we conclude that a substantial number of early stage CKD
patients with GFR ≥ 60 mL/min/1.73 m² have a functional abnormality of pulmonary circula-
tion. Plasma BNP, GFR, and LA, all impose an independent influence on Doppler-estimated
PASP. Estimation and follow-up of PASP using echocardiography may be required in CKD
patients even when GFR ≥ 60 mL/min/1.73 m². Periodic measurement of plasma BNP may be a
valuable predictor for monitoring the progression of PH in early stages of CKD.

**Limitations of the study**

The sample size of this study is relatively small, and for this reason, large multicenter
studies are required to confirm our findings. Pulmonary systolic artery pressure was non-
invasively measured using Doppler echocardiography without obtaining right heart catheter-
ization. In addition, we did not collect follow-up data to evaluate the effect of PH on morbidi-
ity and mortality. Further investigations in a large number of stage 1-3 CKD (according to
KDOQI) patients with PH are needed. Long-term follow-up is essential for future studies.
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REFERENCES


Pulmonary hypertension in CKD patients


