Původní sdělení | Original research article

Pulmonary Hemodynamics in Patients with Chronic Kidney Disease before Starting Renal Replacement Therapy

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ARTICLE INFO

Article history:
Submitted: 6. 7. 2023
Revised: 9. 10. 2023
Accepted: 14. 11. 2023
Available online: 6. 12. 2023

Klíčová slova:
Chronické onemocnění ledvin
Plíce a hemodynamika
Plicní hypertenze

Keywords:
Chronic kidney disease
Pulmonary hemodynamics
Pulmonary hypertension

SOUHRN

Kontext: Plicní hypertenze (PH) je u pacientů s chronickým onemocněním ledvin (chronic kidney disease, CKD) onemocněním s vysokou prevalencí; současně je spojeno s nepříznivějším výsledným stavem. Řada studií zkoumala u pacientů s CKD při již zavedené náhradě renálních funkcí (renal replacement therapy, RRT) prevalenci PH neinvazivními metodami. K dispozici je však málo údajů o hemodynamických poměrech pacientů s CKD před zahájením RRT.
Účel: Cílem naší studie bylo popsat, s použitím invazivní katetrizace srdce, hemodynamické poměry v plicích u pacientů s CKD ještě před zahájením RRT.
Metody: Před zahájením RRT bylo celkem 95 pacientů s CKD vyšetřeno na možnou přítomnost PH transtorakální echokardiografií; pacientům se středně vysokou až vysokou pravděpodobností PH bylo nabídnuto invazivní vyšetření hemodynamiky.
Výsledky: Echokardiografické vyšetření zjistilo středně vysokou až vysokou pravděpodobnost přítomnosti PH u 37 (39 %) pacientů s CKD v predialýze. Z 21 pacientů, u nichž bylo invazivní vyšetření hemodynamiky provedeno, potvrdila invazivní katetrizace srdce u 19 (90,5 %) diagnózu PH. Medián věku studované populace byl 61 let (22–72); mezi pacienty bylo 57 % žen. U většiny studované populace byla pozorována symptomatická dyspnoe (85,7 %). Postkapilární PH byla přítomna v 16 případech (76,2 %), přičemž u tří pacientů (14,3 %) byla prokázána kombinace pre- a postkapilární PH. Průměrný tlak v plicnici koreloval s tloušťkou mezikomorového septa (p = 0,01), průměrem levé síně (p = 0,03) a s poměrem E/e' (p < 0,001). Echokardiografické ukazatele napětí stěny pravé komory a diastolická dysfunkce byly – ve srovnání s pacienty s postkapilární PH v důsledku dilatace pravé komory (p = 0,001), středně těžké až těžké insuficience trojcípé chlopně (p = 0,01), tloušťky mezikomorové přepážky (p = 0,05) a poměru E/e' (p = 0,03) – u pacientů s kombinovanou pre- a postkapilární PH ovlivněny statisticky významně.
Závěr: V této monocentrické studii byla převládajícím fenotypem PH u pacientů s CKD v predialýze postkapilární PH. Echokardiografické markery diastolické dysfunkce korelovaly s invazivně naměřeným průměrným tlakem v plicnici. Pacienti s kombinací pre- a postkapilární PH vykazovali pokročilejší remodelaci pravé komory a vyšší hodnoty markerů diastolické dysfunkce, což ukazovalo na možnou úlohu terminálního selhání ledvin v remodelaci plicní vaskulatury.

ABSTRACT

Background: Pulmonary hypertension (PH) is a highly prevalent condition in patients with chronic kidney disease and is associated with worse outcomes. Many studies described the prevalence of PH in patients with chronic renal disease on established renal replacement therapy (RRT) by non-invasive methods. However, there is a paucity of data on the peculiar hemodynamic characterization of patients with CKD prior to established RRT.
Purpose: Our study aimed to describe the pulmonary hemodynamics in chronic kidney disease patients before starting established renal replacement therapy by invasive cardiac catheterization.
Methods: A total of ninety-five patients with CKD before starting established renal replacement therapy was assessed for probability of PH by transthoracic echocardiography, patients with an intermediate to high probability of PH by transthoracic echocardiography were offered invasive hemodynamic evaluation.

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DOI: 10.33678/cor.2023.083

Please cite this article as: Bekhit F, Baghdady Y, Hassanin N, et al. Pulmonary Hemodynamics in Patients with Chronic Kidney Disease before Starting Renal Replacement Therapy. Cor Vasa 2023;65:837–842.

Results: Thirty-seven (39%) pre-dialysis CKD patients had an intermediate to high echocardiographic probability of PH. Out of the twenty-one patients who proceeded to invasive hemodynamic study; nineteen (90.5%) patients had a confirmed diagnosis of pulmonary hypertension (PH) by invasive cardiac catheterization. The median age of the studied population was 61 years (22–72). Female gender represented 57% of patients. Most of the studied population had symptomatic dyspnea (85.7%). Post-capillary PH was present in 16 cases (76.2%); whereas 3 patients (14.3%) had a combined pre- and post-capillary PH. Mean pulmonary artery pressure was positively correlated with interventricular septal wall thickness (p-value = 0.01), left atrial diameter (p-value = 0.03) and E/e' ratio (p-value <0.001). Echocardiographic indices of right ventricular strain and diastolic dysfunction were significantly affected in patients with combined pre- and post-capillary PH as compared to patients with post-capillary PH such as RV dilatation (p = 0.001), moderate to severe tricuspid incompetence (p = 0.01), septal wall thickness (p = 0.05), and E/e' (p = 0.03).
Conclusion: In this single-center study, post-capillary PH was the predominant phenotype of PH in pre-dialysis CKD patients. Echocardiographic markers of diastolic dysfunction were positively correlated with the invasively measured mean pulmonary artery pressure. Patients with combined pre- and post-capillary PH had a more progressive right ventricular remodeling and higher levels of markers of diastolic dysfunction suggesting the possible role of end stage renal disease on remodeling the pulmonary vasculature.

Introduction

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in patients with chronic kidney disease whether or not on renal replacement therapy.[1] CVD is present in >50% of patients undergoing dialysis and the relative risk of death due to cardiovascular (CV) events in HD patients is 20 times higher than in the general population. Pulmonary hypertension (PH) is a highly prevalent condition in patients with CKD and is significantly associated with worse outcomes.[2,3] Patients with chronic kidney disease starting renal replacement therapy exhibit peculiar hemodynamic features that haven't been well studied. Most of the previous studies except for one prospective study[4] used non-invasive methods to evaluate the prevalence of pulmonary hypertension in patients with pre-dialysis CKD despite the fact that right heart catheterization is the gold standard method to both confirm the diagnosis and describe the phenotype of the disease.

Patients and methods

Our prospective single center study recruited patients with CKD stage starting permanent renal replacement therapy admitted to the Nephrology Department, Cairo University over two years period from April 2018 to April 2020. Local ethics committee approval was obtained prior to patients recruitment. Written informed consent was obtained from all participants involved in our study. Inclusion criteria were the following: Adults >18 years old, CKD (defined as glomerular filtration rate [GFR] <30 ml/min/1.73 m^2 assessed by MDRD4-formula)[5] scheduled for initiating permanent renal replacement therapy and a possible or probable diagnosis of PH by transthoracic echocardiography according to the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of PH.[6]

Exclusion criteria were as follows: uncontrolled arterial hypertension (defined as repeated blood pressure measurements before entry into the study >180/110 mmHg), current malignant diseases, pregnancy, left ventricular ejection fraction (LVEF) <50%, congenital heart disease, organic valvular heart disease causing more than mild regurgitation or stenosis, active myocarditis, endocarditis, pericarditis, hemoglobin concentration <7 g/dl, severe chronic obstructive pulmonary disease (COPD) defined by forced expiratory volume FEV_1 <60% predicted, interstitial lung disease, or known PAH diagnosis or receiving PAH specific medication. Patients with established arteriovenous fistulas were excluded. All eligible patients underwent detailed clinical, laboratory, and echocardiographic evaluation and all enrolled patients had invasive hemodynamic assessment by right and left heart catheterization.

Transthoracic echocardiographic study

Transthoracic echocardiography was performed including standard two-dimensional, M-mode, pulsed wave Doppler, and tissue Doppler modalities. The following measurements were taken: Left ventricular internal dimensions, left ventricular ejection fraction, anteroposterior left atrial dimension by M-mode method and the average E/e' ratio by pulsed wave Doppler of the mitral inflow and tissue Doppler imaging (TDI) of the medial and lateral aspects of the mitral annulus. Assessment of right ventricular function was done by measurement of fractional area change (2D FAC) and tricuspid annular plane systolic excursion (TAPSE). Right ventricular dilation was determined by confirming the presence of basal RV/LV ratio >1.0. Enlarged right atrial area is defined as >18 cm^2 in the four-chamber view. The presence or absence of pericardial effusion was assessed.

Tricuspid regurgitation maximal velocity was used to determine RV systolic pressure, which is considered equal to PASP in the absence of pulmonary outflow tract obstruction and/or pulmonic valve stenosis by calculating the systolic trans-tricuspid gradient using the modified Bernoulli equation (as simplified by Hatle et al.) and then adding a calculated right atrial pressure (RAP) by obtaining the diameter of inferior vena cava (IVC) and its respiratory collapsibility.[7]

Invasive hemodynamic catheterization

All catheterization measurements were performed in the supine position at rest using fluoroscopic guidance with standard techniques using a 6F fluid-filled, single-

-lumen catheters. The following pressure measurements were taken: mean right atrial pressure, pulmonary artery pressures (systolic, diastolic, mean PAP), transpulmonary pressure gradient (TPG), diastolic pulmonary vascular pressure gradient, pulmonary and systemic vascular resistance in wood units, systemic arterial pressure (systolic, diastolic, mean PAP) and left ventricular end diastolic pressure. Cardiac index was calculated using Fick method. All measurements were taken at end expiration with an average of three readings, and patients were in room air.

The recently introduced definition and classifications of PH were adopted for the analysis of the results.[1] Postcapillary PH was defined as mPAP >20 mmHg, PAWP >15 mmHg, PVR ≤2 WU. Precapillary PH was defined as mPAP >20 mmHg, PAWP ≤15 mmHg, PVR >2 WU. Combined pre- and postcapillary PH was defined as mPAP >20 mmHg, PAWP >15 mmHg and PVR >2 WU. The presence of any of the following hemodynamic features categorize higher risk patients as stated by the recent European guidelines of PH:[6] RAP >14 mmHg, CI <2.0 L/min/m^2 or SVO_2 <60%. Pulmonary vasoreactivity testing is only recommended in patients with idiopathic pulmonary arterial hypertension (PAH), heritable, or drug induced PAH to evaluate their candidacy for calcium channel blocker treatment. Our patients, who belonged to the multifactorial group five pulmonary hypertension, were not eligible for vasoreactivity testing as there is no proven benefit of CCB in this subpopulation.[6]

Statistical analysis

Statistical analysis was performed using a statistical software program (SPSS-18 statistical package program). Data were presented as mean ± SD, controlled for normal distribution by the Kolmogorov–Smirnov test. Differences between groups were compared with Student's t-test and Mann–Whitney U test, as applicable. Chi-square test was used to estimate the occurrence of categorical variables. Two-tailed bivariate correlations were determined by the Pearson's coefficient. Statistical significance was set at p <0.05.

Results

A total of ninety-five patients presenting with chronic kidney disease stage 4 or 5 (defined as GFR <30 ml/min/1.73 m^2 assessed by MDRD4-formula) were assessed for eligibility. Thirty-seven patients (39%) had an intermediate/high probability of PH by TTE. Only twenty-one patients approved to participate in the study and proceeded to invasive hemodynamic assessment by cardiac catheterization. A flow chart of the studied population is illustrated in Figure 1.

Baseline clinical and laboratory data

Table 1 shows the clinical, laboratory and CKD characterization of the studied population. Thirteen patients were above the age of 60 years and seven patients were aged 45–60 years. Twelve patients (57%) had an abdominal obesity defined as body mass index (BMI) ≥30 kg/m^2. Seventy-six percent of the studied population had symptomatic dyspnea. Two patients had an underlying heredita-

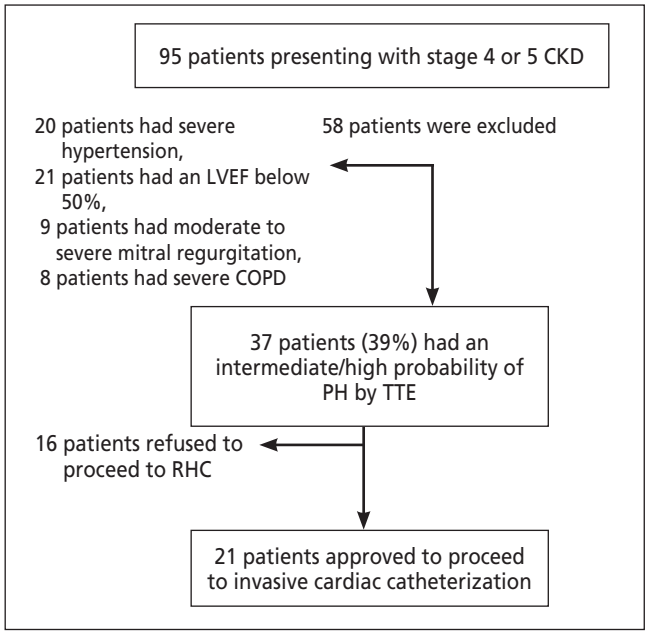

Fig. 1 – Flow chart of the studied population.

Table 1 – Baseline characteristics of the study population

Characteristics	Patients
Age	61 (22–72)
Female gender	12 (57.1%)
Diabetes	8 (38.1%)
Hypertension	17 (81%)
Coronary artery disease (CAD)	1 (4.8%)
Cerebrovascular disease (CVS)	3 (14.3%)
Smoking	7 (33.3%)
Body mass index	32 (21–42)
Dyspnea (WHO class I–IV) WHO I WHO II WHO III WHO IV	 5 (23.7%) 1 (4.8%) 9 (42.9%) 6 (28.6%)
Treatment Beta-blockers Calcium channel blockers	 13 (61.9%) 10 (47.6%)
Blood urea (mg/dL)	145 (52–310)
Blood creatinine (mg/dL)	8.4 (2.5–10.6)
eGFR (mL/min/1,73 m^2)	7 (4–28)
Hemoglobin (g/dL)	9 (7.4–11)
Serum potassium (mmol/L)	4.4 (3.6–5.6)
Duration of follow up in the Nephrology Department with chronic renal disease (months)	6 (3–60)
Etiology of CKD Hypertension Diabetes Hereditary Obstructive uropathy	 16 (76.2%) 2 (9.5%) 2 (9.5%) 1 (4.8%)

Data are presented as number (%) of patients for categorical variables, and median (range) for continuous variables.

Table 2 – Echocardiographic data in the study population

Echocardiographic variable	
Left ventricular end diastolic dimension (mm)	50 (35–58)
Left ventricular end systolic dimension (mm)	32 (23–36)
Interventricular septal wall thickness (mm)	11 (8–17)
Left atrial diameter (mm)	41 (32–60)
Ejection fraction (%)	66 (54–74)
Pulmonary artery systolic pressure (PASP) (mmHg)	48 (39–90)
Tricuspid regurgitation maximal velocity (TR V_{max}) (m/s)	3.4 (3.0–4.4)
Fractional area change of the right ventricle (%)	43 (36–56)
Right ventricular enlargement	5 (23.8%)
Tricuspid annular plane systolic excursion (TAPSE) (mm)	24 (17–32)
Inferior vena cava diameter (mm)	18 (±4)
Tricuspid incompetence; number (%) Mild Moderate Severe	 15 (71.4%) 5 (23.8%) 1 (4.8%)
Mitral incompetence; number (%) Mild Moderate	 10 (47.6%) 2 (9.5%)
Pericardial effusion (mild); number (%)	3 (14.3%)
E/e'	8.1 (7–15)

Data are presented as number (%) of patients for categorical variables, and median (range) for continuous variables.

Table 3 – Hemodynamic data in the study population

Characteristics	Median (range)
Heart rate (bpm)	80 (60–120)
Systolic arterial pressure (mmHg)	140 (100–160)
Diastolic arterial pressure (mmHg)	80 (60–100)
Mean arterial pressure (mmHg)	106 (73–120)
Cardiac output (L/min)	4.9 (3.1–8.5)
Cardiac index (L/min/m^2)	2.5 (1.6–4.3)
Right atrial pressure (mmHg)	8 (4–21)
Systemic vascular resistance (WU)	18 (9–32)
Pulmonary artery systolic pressure (mmHg)	41 (27–90)
Pulmonary artery diastolic pressure (mmHg)	19 (9–30)
Mean pulmonary artery pressure (mmHg)	27 (17–50)
Left ventricular end diastolic pressure (mmHg)	16 (10–34)
Trans-pulmonary gradient (mmHg)	10 (4–25)
Pulmonary vascular resistance (WU)	2 (1–7)

Data are presented as median (range) for continuous variables.

Table 4 – Pulmonary hypertension by invasive hemodynamic cardiac catheterization

	PH number (%)	No PH number (%)
PAP >20 mmHg Post-capillary Combined (pre- and post-capillary) Pre-capillary	19 (90.5%) 16 (76.2%) 3 (14.3%) 0	2 (9.5%)

ry renal disease (one with adult polycystic kidney disease and another patient had oxalosis). Only five patients had hemoglobin values below 9 g/dL. Two patients had stage IV CKD (an estimated GFR 15–30 ml/min/1.73 m^2), the rest of patient had stage V CKD.

Echocardiographic data

Table 2 shows the echocardiographic data of the study population. Seven patients had an intermediate likelihood of PH by echocardiography, 14 patients had a high likelihood of PH. Seventeen patients (81%) had left atrial enlargement (left atrial diameter is 40 mm or more). Fourteen patients (67%) had concentric left ventricular hypertrophy (septal wall thickness is 11 mm or more).

Invasive hemodynamic cardiac catheterization

Our patients underwent hemodynamic assessment one or two days after echocardiographic evaluation. Tables 3 and 4 illustrate the results of invasive hemodynamic assessment. Pulmonary hypertension was present in 19 patients (90.5%) when mPAP >20 mmHg was the diagnostic cut-off and was observed in 13 (61.9%) patients when mPAP ≥25 mmHg was used to make the diagnosis of PH. Postcapillary PH was diagnosed in 16 cases (76.2%); whereas combined pre- and post-capillary PH without vasoreactivity testing was found in 3 cases (14.3%). The two patients who turned out not to have PH by invasive assessment had an intermediate likelihood of PH with TR maximal velocities of 2.9 and 3 m/s.

Higher risk patients included two patients with all the three features of a low cardiac index below 2 L/min/m^2, low mixed venous oxygen saturation less than 60%, and a high right atrial pressure more than 14 mmHg, two patients had two criteria and four patients had at least one high risk criterion. Intermediate risk patients included night patients with one of the following criteria: a cardiac index between 2.0–2.4 L/min/m^2, a mixed venous oxygen saturation range of 60–65%, and a right atrial pressure range of 8–14 mmHg. Four patients were at a lower risk.

Comparison between patients with post-capillary PH and combined pre- and post-capillary PH

Table 5 shows the differences between the two groups of patients regarding their clinical, laboratory, and echocardiographic characteristics.

Patients with combined pre- and post- capillary PH were of a relatively younger age (p = 0.03). Echocardiographic indices of right ventricular strain (RV dilatation [p = 0.001], moderate to severe tricuspid incompetence [p = 0.01]) were present in the three patients. Markers of diastolic dysfunction (septal wall thickness [p = 0.05], and E/e' [P = 0.03]) were also significantly higher when compared with patients with isolated post-capillary PH.

There was a trend towards shorter duration of follow up (p = 0.07).

Table 5 – Comparison between patients with post-capillary PH and combined pre- and post-capillary PH

Variable	Post-capillary PH	Combined pre- and post-capillary PH	*p*-value
Clinical variables			
Age	61.5 (51.8–65)	60 (58–60)	**0.03**
Age >65 years	5	0	**0.06**
Female gender	10	2	0.23
Diabetes mellitus	6	2	0.32
Hypertension	13	3	0.38
Obesity (BMI >30 kg/m^2)	10	2	0.23
Duration of follow up in the Nephrology Department (months)	24 (4–34)	4 (3–4)	**0.07**
Laboratory work			
Serum creatinine (mg/dL)	8.4	6.6	0.21
Blood urea (mg/dL)	143 (131–185)	154 (122–154)	0.22
Hemoglobin (g/dL)	9 (8.6–9.5)	9 (9)	0.72
Echocardiographic data			
LVEDD (mm)	51.5 (45.3–57)	50 (45–50)	0.42
IVS (mm)	11 (10–13)	15 (14–15)	**0.03**
LAD (mm)	41 (36–47.8)	46 (45–46)	0.16
LAD >40 mm	12	3	0.462
LVEF (%)	66.5 (60.1–69.8)	65 (65)	0.42
TR V_{max} (m/sc)	3.3 (3.1–3.5)	3.6 (3.6)	**0.05**
FAC (%)	44 (40.5–48.5)	40 (36–40)	0.60
TAPSE (mm)	25 (23–27.8)	22 (17–22)	0.50
RV dilatation	1	3	**0.001**
Moderate MR	1	1	0.304
Moderate and severe TR	3	3	**0.011**
E/e'	8 (7.1–10.4)	13 (12.2–13)	**0.08**
Invasive variables			
mPAP	26.5 (21.3–33.5)	40 (29–40)	**0.01**
CI	2.7 (2.2–3.7)	1.9 (1.9–2.0)	0.10
RAP	8 (7–10.8)	14 (5–14)	0.25
LVEDP	18.3	17.5	0.23

* Data are presented as number (%) of patients for categorical variables, and median (range) for continuous variables.

It was noticed that patients with combined PH had also significantly higher levels of mean pulmonary artery pressure ($p = 0.01$), numerically lower invasively measured cardiac index, and higher right atrial pressures. The three patients had hypertension and two of them were diabetics. All the three patients presented with dyspnea at rest.

Discussion

According to our knowledge, this is the second prospective study evaluating the prevalence of PH by the use of invasive hemodynamic assessment in patients with CKD. At the start of our research we relied on the fifth World Symposium on PH (2013)[6,8,9] to define pulmonary hypertension as mPAP ≥25 mmHg. However, during the preparation of the manuscript, the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension lowered the cut-off value for defining PH as mPAP >20 mmHg.

One advantage of our study is the use of invasive methodology, the "gold standard" for the assessment of hemodynamic impairment and differential diagnosis between pre- and post-capillary PH,[10] for all study participants who had a probability of PH by transthoracic echocardiographic screening. Another advantage of our study is the use of left ventricular (LV) end-diastolic pressure which is considered the gold standard for the diagnostic definition of the phenotype of pulmonary hypertension, rather than pulmonary capillary wedge pressure because it has s superior diagnostic accuracy in patients with elevated left ventricular filling pressures.[11] We selected patients with chronic kidney disease stage just before initiating established renal replacement therapy for three months to exclude the hemodynamic effects of chronic dialysis and arteriovenous fistulas on the pulmonary circulation. Our pre-dialysis CKD patients had a 39% prevalence of intermediate to high echocardiographic probability of pulmonary hypertension, similar to the reported prevalence of PH in CKD populations in different previous non-invasive studies.[12–14] Our patients had a higher frequency of worsening dyspnea (NYHA class IV), which could be due to the selection of patients who were recruited for invasive hemodynamic assessment just before starting renal replacement therapy, and this may have contributed to the higher volume overload conditions, and explained why our studied

population had a predominant phenotype of post-capillary PH and a lower eGFR compared with conservatively managed CKD patients without dialysis in the PEPPER study.[4] In our study, the prevalence of PH was higher than the other three studies (90.5%) for two reasons. First, patients underwent the procedure on the basis of the echocardiographic likelihood of PH. Second, we implemented the new definition of PH with a cut-off of mPAP >20 mmHg to confirm the diagnosis of PH. In this study, the prevalence of post-capillary PH was found to be 76.2% similar to patients enrolled in the PEPPER study (80%). This can be attributed to the high prevalence of comorbidities causing both CKD and post-capillary PH (e.g. hypertension and diabetes), high cardiac output resulting from anemia of renal disease, left ventricular diastolic dysfunction, as well as from fluid retention.[15–17] Combined pre- and post-capillary PH was found in 14.3% of the examined CKD patients. They were of a relatively younger age. Echocardiographic indices of right ventricular strain (RV dilatation, moderate to severe tricuspid incompetence) were present in all the three patients. Markers of diastolic dysfunction (TR V_{max}, septal wall thickness and E/e') were also significantly higher when compared with patients with isolated post-capillary PH. There was a trend towards shorter duration of CKD diagnosis. Features of a higher risk by hemodynamic assessment (higher levels of mean pulmonary artery pressure, lower cardiac index, and higher right atrial pressures) reflect the possibility that those patients exhibited the disease at an earlier age with markedly uncontrolled risk factors and rapid progression of the disease that caused irreversible pulmonary vascular changes and RV remodeling.

Conclusion

In this single-center study, it was observed that PH is a prevalent disease, yet under-recognized co-morbidity among patients with pre-dialysis CKD who are referred for invasive hemodynamic catheterization. Post-capillary PH was the predominant phenotype of PH in CKD patients. Echocardiographic findings suggest the possible role of diastolic dysfunction in the development of PH in CKD patients. Fewer patients had combined pre- and post-capillary PH with more progressive right ventricular remodeling and higher levels of markers of diastolic dysfunction suggesting the possible effects of end stage renal disease on remodeling the pulmonary vasculature and increased pulmonary vascular resistance.

Limitations

Our study was limited by the small sample size of the studied population. Invasive hemodynamic measurements were taken just before renal replacement therapy was established, thus volume overload may have contributed to the higher prevalence of pulmonary hypertension. A significant proportion of patients had a moderate degree of anemia which may have contributed to the prevalence of pulmonary hypertension in the studied population. Measurement of CI was done by the use of direct Fick method, which has its own pitfalls.

Conflict of interest

There is no conflict of interest in our study.

Ethical statement

The study received ethical approval by the Faculty of Medicine, Cairo University.

Informed consent

Written informed consent was obtained from all participants involved in our study.

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