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RESEARCH ARTICLE

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Hemodynamic response to inhaled nitric oxide in patients with pulmonary hypertension and chronic kidney disease: A retrospective cohort study

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Abstract

Pulmonary hypertension (PH) associated with chronic kidney disease (CKD) (PH-CKD) affects approximately 20%–40% of CKD patients and is associated with increased morbidity and mortality. PH and CKD are both pathophysiologically associated with nitric oxide (NO) deficiency. The NO pathway, an important therapeutic domain in pulmonary arterial hypertension (PAH), is an intriguing but unexplored target in PH-CKD. We sought to improve understanding of the clinical significance of the NO pathway in patients with PH-CKD by assessing the hemodynamic response to inhaled NO (iNO) during right heart catheterization (RHC). In this retrospective cohort study, patients with diagnosis codes of PH and stage IV/V CKD or end-stage renal disease and estimated glomerular filtration rate < 60 mL/min/body surface area who underwent RHC and hemodynamic drug study between July 2011 and June 2021 were eligible. Patients with mean pulmonary artery pressure (mPAP) $>$ 20 mmHg and pulmonary vascular resistance (PVR) > 3 Wood units were included. The final cohort included 37 patients (45.9% female, mean age 72.5 ± 9.7 years). A total of 56.7% of the cohort (21/37) had precapillary PH, while 43.2% (16/37) had combined precapillary postcapillary PH (Cpc-PH). Median survival was 3.1 years after RHC. iNO was associated with a significant decrease in both mPAP and PVR. Hemodynamic changes in mPAP and PVR were similar in precapillary and Cpc-PH groups. Among a small subset ($n = 14$) who were subsequently treated with PAH-targeted therapy, treatment response was mixed and did not reveal significant benefit. Further studies are warranted to better define the potential role of PAH therapy in PH-CKD.

KEYWORDS
combined precapillary postcapillary PH, precapillary PH, right heart catheterization

INTRODUCTION

Chronic kidney disease (CKD) affects an estimated 37 million adults in the United States and can progress to end-stage renal disease (ESRD) requiring dialysis and/or kidney transplant (KT).[1] Pulmonary hypertension (PH), classically defined as an elevated mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, affects 21%–40% of patients with CKD and one-third of KT candidates.[2–5] PH associated with CKD (PH-CKD) is classified as Group 5 PH due to its multifactorial and/or unclear mechanisms.[6] PH-CKD can be due to an increase in pulmonary vascular resistance (PVR), cardiac output (CO), pulmonary artery wedge pressure (PAWP), or a combination of factors.[3] While mPAP elevations secondary to PAWP are common in CKD, approximately 60% of patients with PH-CKD have an increased PVR, suggesting the presence of intrinsic pulmonary vascular disease and pulmonary vascular remodeling.[7]

Importantly, PH in CKD has significant prognostic implications. It is associated with worse outcomes, including both worse survival and increased hospitalizations.[4,8–11] Among KT recipients, PH is independently associated with more than threefold increased risk of posttransplant death[12] and increased risk of graft dysfunction.[13] Moreover, the presence of CKD is associated with worse survival and increased hospitalizations among pulmonary arterial hypertension (PAH) patients.[5,14] This relationship between PH and CKD underscores the importance of improved understanding of the pathobiology of PH-CKD and subsequent identification of novel treatment pathways.

PH and CKD are both pathophysiologically associated with nitric oxide (NO) deficiency, as well as endothelial dysfunction and renin–angiotensin–aldosterone activation.[3,15] The NO pathway, an important therapeutic domain in PAH and chronic thromboembolic PH (CTEPH), is an intriguing but unexplored target in PH-CKD.[16] Our primary aim was to improve understanding of the clinical significance of the NO pathway in patients with PH and CKD by assessing hemodynamic response to inhaled NO (iNO) during right heart catheterization (RHC). Toward this aim, we assessed the acute hemodynamic response to iNO in patients with concurrent PH and CKD. We hypothesized that there would be a significant improvement in pulmonary hemodynamics (mPAP, PVR) with iNO administration. Additionally, we evaluated the clinical response to therapy in those patients who received PAH-targeted treatment following RHC.

METHODS

Study design

We performed a retrospective cohort study. The electronic health records (EHR) from two sites within the same academic health system (Mayo Clinic facilities in Rochester, Minnesota, and Jacksonville, Florida) were searched to identify patients with diagnosis codes of PH (SNOMED CT code of pulmonary hypertension, ICD 9: 416.0; ICD 10: I27.2X) and either stage IV/V CKD or ESRD (SNOMED CT code of Stage IV/V CKD or ESRD, ICD 9: 403.1, 403.91, 585.6; ICT 10: I13.2, N18.4, N18.5, N18.6) who underwent RHC with hemodynamic drug study between July 2011 and June 2021. We excluded patients who did not receive iNO, patients with an estimated glomerular filtration rate (eGFR) >60 by chronic kidney disease epidemiology collaboration-Creatinine 2021 calculation within 1 year of RHC (despite listed ICD CKD/ESRD diagnoses in EHR), a history of complex congenital heart disease (corrected or uncorrected), and patients with mPAP < 21 mmHg or PVR < 3 Wood units (WU). This study was approved by the institutional review board (Mayo Clinic, IRB 20-008842).

Hemodynamic data

RHCs were performed per usual clinical protocol for each institution. iNO was administered at a dose of 20–80 ppm with repeat assessment of pulmonary hemodynamics. Hemodynamic data was collected from RHC reports via manual review of the EHR. If an individual patient underwent multiple RHCs during the study period, we included results only from earliest RHC. Variables collected and analyzed include mean right atrial (RA) pressure (mmHg) and mPAP (mmHg), PVR (WU), PAWP (mmHg), and CO (L/min) both at baseline and with iNO administration. CO was obtained by either thermodilution or Fick method at the discretion of the performing proceduralist. Precapillary PH was defined as mPAP > 20 mmHg and PVR ≥ 3 WU with PAWP ≤ 15 mmHg, and combined precapillary postcapillary PH (Cpc-PH) was defined as mPAP > 20 mmHg and PVR ≥ 3 WU with PAWP > 15 mmHg per hemodynamic criteria at time of RHC and analysis.[6] Formal vasoreactivity criteria (hemodynamic response to iNO administration) were defined per current guidelines as a decrease in mPAP ≥ 10 mmHg to ≤40 mmHg with an increased or unchanged CO.[6] In this study, patients meeting these criteria are referred to as "vasoresponders" and those who do not as "nonresponders." Of note, iNO was administered during RHC per the request of the referring provider.

Survival

Vital status was assessed for all individuals from review of the EHR. Patients were censored at death, last follow-up or 12/31/21, whichever occurred first. Median survival was determined for the cohort from the time of RHC, and overall survival in patients with precapillary PH and Cpc-PH and vasoresponders and nonresponders were compared.

Treatment group and follow-up

Patients prescribed PAH-targeted therapies (phosphodiesterase 5-inibitors [PDE5-i], endothelin receptor antagonists, prostacyclin pathway agents, soluble guanylate cyclase [sGC] stimulators) at the discretion of their treating clinician were further described in a subgroup analysis. Those with follow-up clinical assessments within 3–12 months were evaluated for treatment response, as determined by the change in N-terminal pro-B-type natriuretic peptide (NT-proBNP), 6-min walk distance (6MWD), New York Heart Association (NYHA) functional class, and transthoracic echocardiogram (TTE). Specific TTE parameters analyzed included right ventricular systolic pressure (RVSP; mmHg), tricuspid regurgitation velocity (m/sec), right ventricular (RV) strain, and qualitative assessment of RV systolic function (normal/mild dysfunction, mild-moderate/moderate dysfunction, or moderate-severe/severe dysfunction). Patient-reported improvement, stability, or worsening in symptoms following initiation or augmentation of PAH therapy was also reported when available.

Statistical methods

Categorical variables were summarized as frequencies and proportions and continuous variables were summarized as means and standard deviations for normally distributed data and median (interquartile range) for nonparametric data. Baseline and post-iNO hemodynamics were compared using a paired t-test. Hemodynamic responses to iNO between subgroups were compared using Wilcoxon rank sum test. Treatment response parameters within individuals were evaluated using paired Wilcoxon signed rank testing and chi-square or Fisher exact test as appropriate. Overall survival was assessed using Kaplan–Meier curves with 95% confidence interval (CI) bands for all included patients. Overall survival in precapillary PH versus Cpc-PH and vasoresponders versus nonresponders was compared using log-rank testing. Statistical analysis was performed in SAS Version 9.4 (SAS institute) and BlueSky program.

RESULTS

Subjects

Initial search of the EHR yielded 118 distinct RHC reports. Of these, 81 were excluded: 34 did not receive iNO, 20 did not have an eGFR < 60 within 1 year of RHC, 19 did not meet hemodynamic criteria (i.e., mPAP <21 mmHg or PVR < 3 WU), four had complex congenital heart disease, and four were subsequent RHCs from the same patient. Thirty-seven patients were included in our final analysis. The flow diagram of patients included and excluded is shown in Figure 1.

The final cohort was 45.9% female with mean age of 72.5 ± 9.5 years. Fifty-seven percent (21/37) had precapillary PH while 43.2% (16/37) had Cpc-PH. Roughly 30% (11/37) had alternative etiologies of PAH (e.g., connective tissue disease) or CTEPH based on review of the EHR (Table 1). Mean baseline creatinine and eGFR were 1.6 and 43.8, respectively. Eight percent (3/37) were on vasodilator therapy at the time of RHC. Nearly three-quarters (74.3%) of the cohort had NYHA functional class 3 or 4 symptoms. Baseline TTE data demonstrated a mean RVSP of 71.9 mmHg with more than half of patients (55.5%) having moderate or severe RV systolic dysfunction (Table 1). See Table 1 for complete details regarding baseline characteristics.

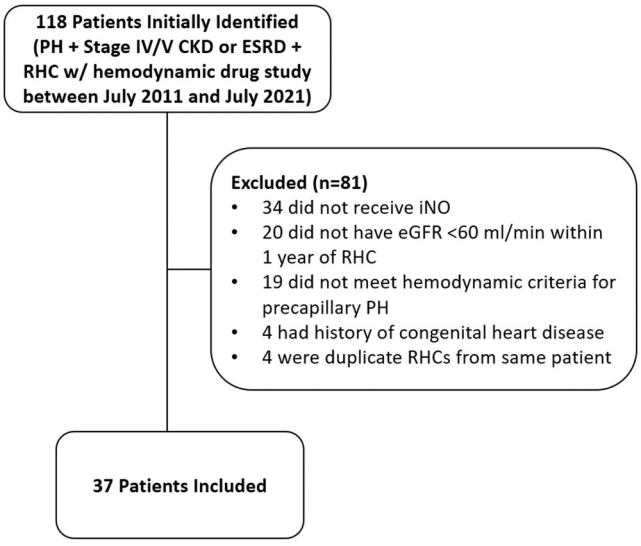

FIGURE 1 Flow diagram of patients included and excluded in final analysis.

TABLE 1 Baseline characteristics.

Baseline characteristics	Cohort ($n = 37$)
Age, years	72.5 ± 9.7
Female sex	17/37 (45.9%)
Precapillary PH	21/37 (56.8%)
Combined pre- and postcapillary PH	16/37 (43.2%)
Alternative etiologies of PAH or CTEPH	11/37 (29.7%)
Connective tissue disease	$n = 6$
CTEPH	$n = 2$
Other	$n = 3$
Renal disease	
On hemodialysis	1/37 (2.7%)
On peritoneal dialysis	0/57
AV fistula	1/37 (2.7%)
Ever underwent kidney transplant (before or after RHC)	1/37 (2.7%)
Creatinine	1.6 ± 0.6 ($n = 37$)
eGFR by 2021 CKD-EPI calculator	43.8 ± 11.6
DM	12/37 (32.4%) (all Type 2 DM)
On vasodilator therapy	3/37 (8.1%)
PDE5 monotherapy	1/37 (2.7%)
Combination (incl PDE5)	2/37 (5.4%)
6MWD (m)	209.8 ± 110.6 ($n = 19$)
Nt-ProBNP (pg/mL)	4551.8 ± 6385.4($n = 37$)
Functional class (NYHA)	
1 or 2	9/35 (25.7%)
3 or 4	26/35 (74.3%)
TTE parameters	
RVSP (mmHg)	71.9 ± 20 ($n = 34$)
TR velocity (m/sec)	3.8 ± 0.6 ($n = 36$)
RV systolic function	
Normal/mild dysfunction	16/36 (44.4%)
Moderate/severe dysfunction	20/36 (55.6%)
RV strain	$-16.8\% \pm 4.4$ ($n = 17$)
Pericardial effusion	9/37 (24.3%)
RA pressure (mmHg)	11.3 ± 6.0

Abbreviations: 6MWD, 6-min walk distance; AV, arteriovenous; CKD, chronic kidney disease; CTEPH, chronic thromboembolic PH; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EPI, epidemiology collaboration; Nt-ProBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDE5; phosphodiesterase 5; PH, pulmonary hypertension; RA, right atrial; RHC, right heart catheterization; RV, right ventricular; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram.

TABLE 2 Hemodynamics during RHC, total cohort ($n = 37$).

Hemodynamic variable	Baseline	iNO	Absolute change *Total (n = 37)*	*p* Value
mPAP, mmHg	44.6 ± 10.5	38.6 ± 9.5	−6.0 ± 5.7	<0.001
PAWP, mmHg	14.4 ± 7.3	15.6 ± 7.7	1.4 ± 3.5	0.02
PVR, WU	7.4 ± 4.3	5.1 ± 3.0	−2.4 ± 2.7	<0.001
CO, L/min	4.5 ± 1.5	5.0 ± 1.8	0.5 ± 1.1	0.02

Abbreviations: CO, cardiac output; iNO, inhaled nitric oxide; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WU, Wood units.

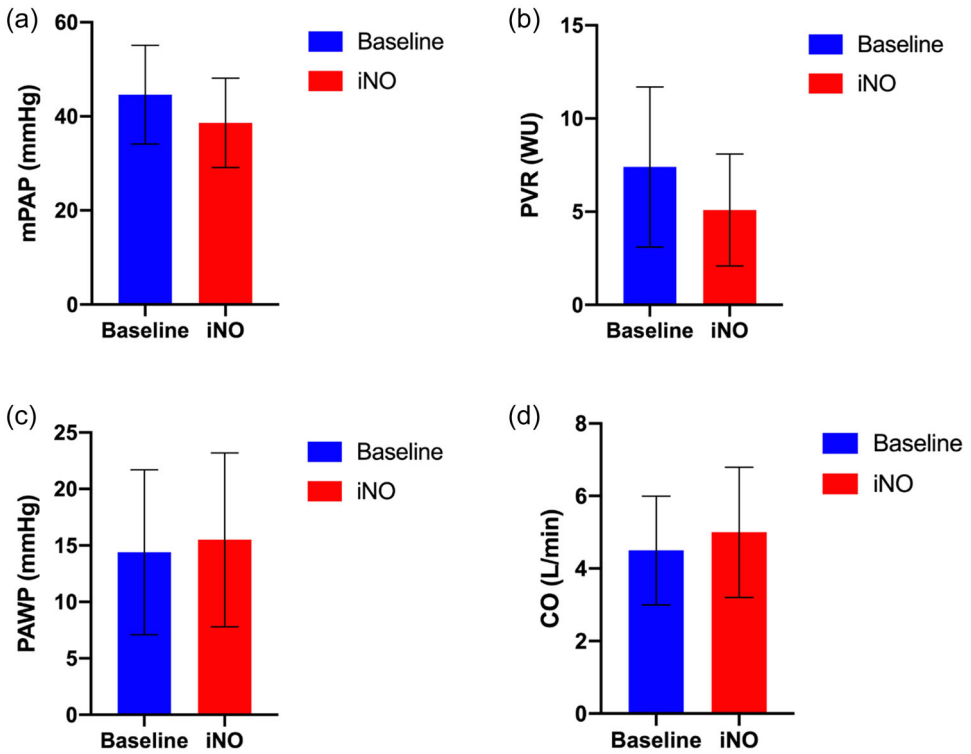

FIGURE 2 Baseline and inhaled nitric oxide pulmonary hemodynamics of overall cohort ($n = 37$).

Hemodynamics

iNO administration was associated with significant decreases in mPAP and PVR. There was an average decrease in mPAP of 6.0 ± 5.7 mmHg ($p < 0.001$) and in PVR of 2.4 ± 2.7 WU ($p < 0.001$) with iNO. There were also small but significant increases in CO and PAWP (Table 2). Twenty-seven percent of patients (10/37) had a decrease in mPAP by ≥10 mmHg with administration of iNO while 11% (4/37) met formal criteria for acute vasoreactivity. Baseline and iNO hemodynamics of the overall cohort are summarized in Figure 2. Hemodynamic changes in mPAP, PAWP, PVR, and CO were similar in precapillary PH and Cpc-PH groups ($p > 0.05$ for all) (Table 3).

TABLE 3 Changes in pulmonary hemodynamics with inhaled nitric oxide administration among hemodynamic subsets.

Hemodynamic variable	Absolute change *precapillary PH (n = 21)*	Absolute change *combined pre- and postcapillary PH (n = 16)*	*p* Value
mPAP, mmHg	−6.4 ± 5.2	−5.5 ± 6.4	0.38
PAWP, mmHg	1.5 ± 2.9	1.4 ± 4.3	0.75
PVR, WU	−2.4 ± 2.6	−2.5 ± 2.9	0.78
CO, L/min	0.5 ± 1.0	0.5 ± 1.3	0.86

Abbreviations: CO, cardiac output; L, liters; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units.

Survival

The overall median survival from the time of RHC was 3.1 years (95% CI 1.4–5.3). Figure 3 shows overall survival for the cohort. There was no significant difference in survival in patients with precapillary versus Cpc-PH (Figure 4). There was also no significant difference in survival in vasoresponders versus nonresponders although NO responsiveness was associated with excellent short-term survival (Figure 5).

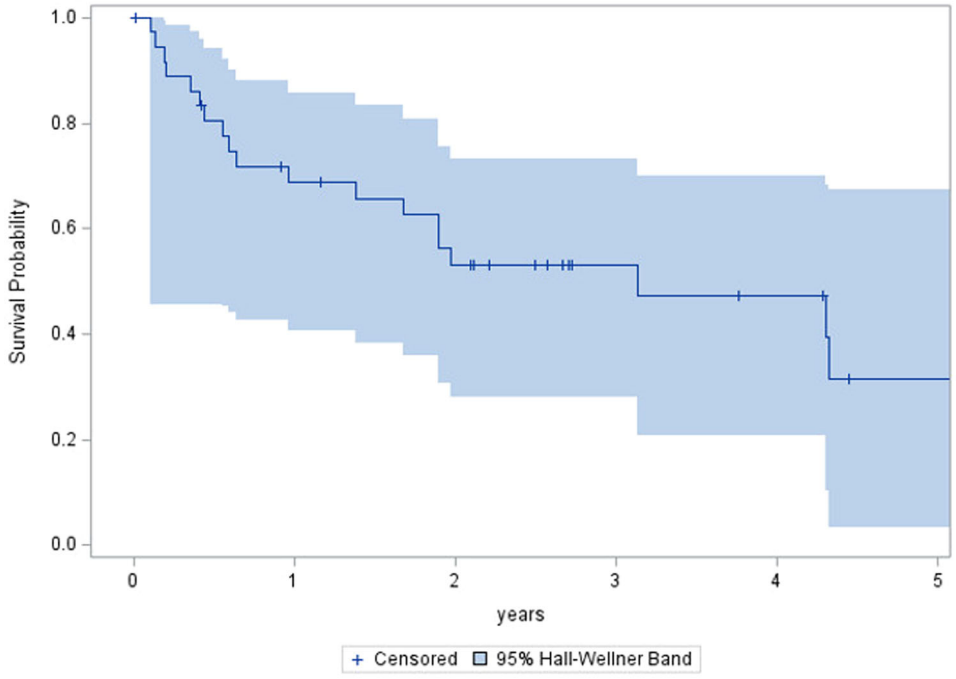

FIGURE 3 Overall cohort survival ($n = 37$).

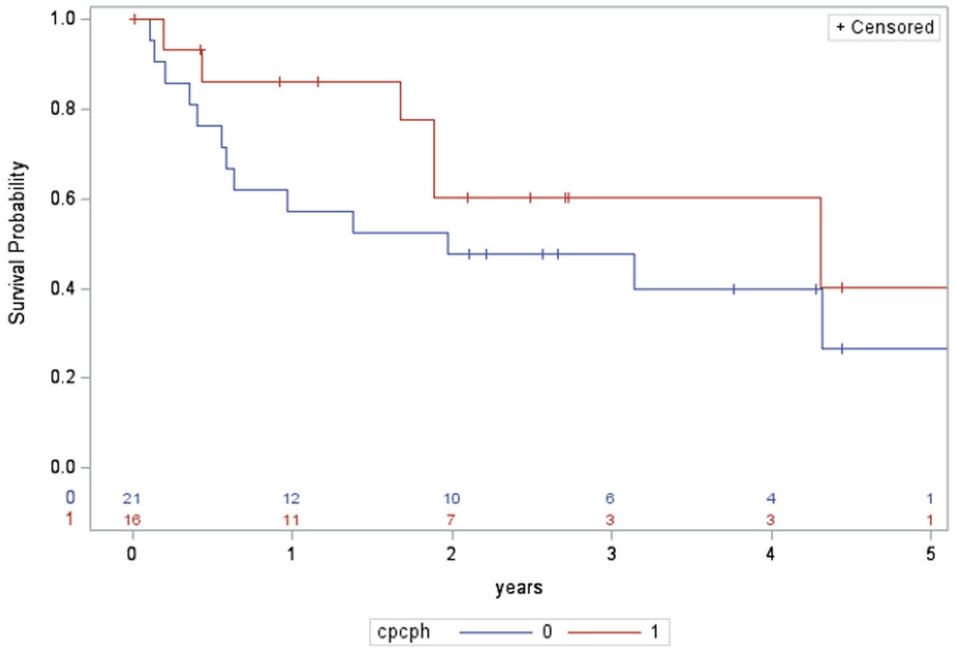

FIGURE 4 Survival: Precapillary versus combined precapillary postcapillary pulmonary hypertension (log-rank $p = 0.21$). CpcPH (red) and precapillary PH (blue).

Treatment group and response at follow-up

Of the 37 patients included in hemodynamic analysis, 23 were subsequently prescribed new or augmented PAH-directed therapy. Of these 23, 14 patients had available follow-up data. Median time to follow up was 122 days. By PAH-targeted therapy class, they were treated as follows: PDE5i monotherapy: 3/14 (21.4%), riociguat monotherapy: 2/14 (14.2%), and combination therapy including PDE5i: 9/14 (64.3%). There was no significant improvement in the defined treatment parameters assessed (6MWD, NYHA functional class, NT-proBNP, TTE parameters) although there was a trend toward improved RV function as assessed by RV strain (Table 4). A majority (64.2%, 9/14) reported symptomatic improvement with PAH therapy. Few (2/14) reported feeling worse symptomatically, and the remaining 3/14 reported no significant change.

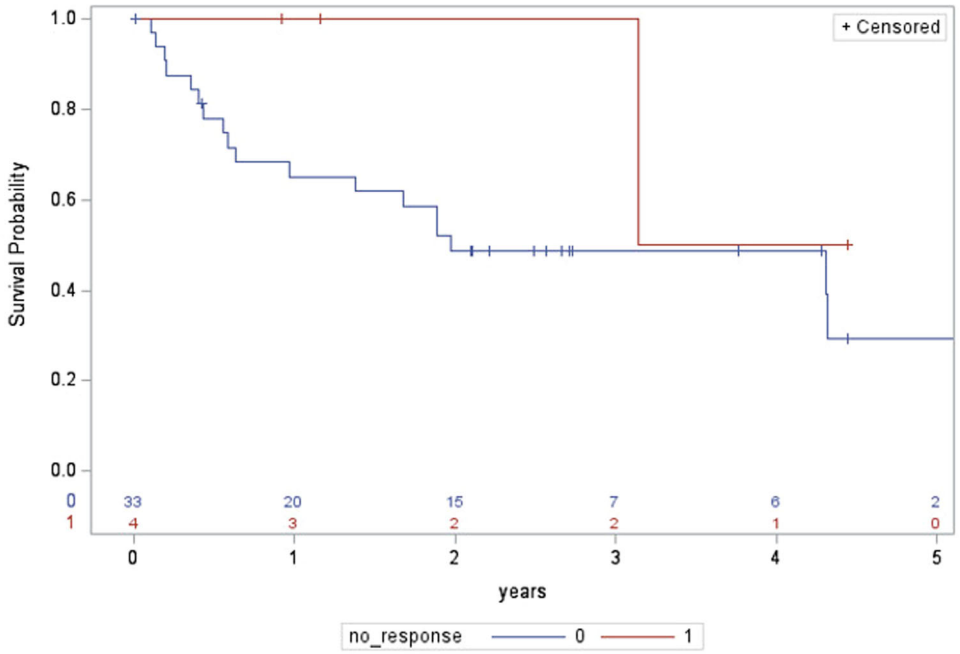

FIGURE 5 Survival among vasoresponders (red) and nonresponders (blue) (log-rank $p = 0.30$).

TABLE 4 Treatment response among 14 patients treated w/available follow-up data.

	Pretreatment	Posttreatment	Delta (post–pre)	*p* Value
6MWD (m) ($N = 5$)	225 ± 40.8	254.2 ± 62.4	29.2 ± 75.8	0.44
NYHA functional class				1.0
1 or 2	4/14 (28.6%)	5/14 (35.7%)	N/A	
3 or 4	10/14 (71.4%)	9/14 (64.3%)		
NT-proBNP (ng/dL) ($N = 12$)	3533.1 ± 3078.9	4068.8 ± 4057.9	535.7 ± 2580.4	0.57
RVSP $N = 10$	72.9 ± 22.8	71.8 ± 20.2	−1.1 ± 18.5	0.87
TR velocity (m/sec) $N = 10$	3.8 ± 0.8	3.9 ± 0.7	0.02 ± 0.05	1.0
RV systolic function				1.0
Normal-mild dysfunction	5/12	4/12	N/A	
Mod-severe dysfunction	7/12	8/12		
RV strain (%) ($N = 9$)	−15.4 ± 4.5	−18.3 ± 4.7	−2.9 ± 3.9	0.07

Abbreviations: 6MWD, 6-min walk distance; NYHA, New York Heart Association; RV, right ventricular; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation.

DISCUSSION

In this retrospective cohort study of 37 patients with PH and CKD, iNO was associated with an acute improvement in pulmonary hemodynamics—specifically, decreased mPAP and PVR—among patients with both precapillary PH and Cpc-PH. Analysis of a small subgroup ($n = 14$) who subsequently received PAH-focused therapy did not show statistically significant improvement in 6MWD, NYHA functional class, or TTE markers of PH severity, although the analysis was limited by the small sample size and a majority of patients reported symptomatic improvement with therapy. Patients in this cohort had a median survival of only 3.1 years following RHC, emphasizing the poor prognosis associated with PH-CKD. To our knowledge, ours is the first study to evaluate the hemodynamic response of patients with precapillary or Cpc-PH and CKD to iNO during RHC. Our findings underscore the therapeutic potential for NO pathway modulation in PH-CKD although multicenter prospective studies are needed to determine the most appropriate treatment approach.

In this cohort of 37 patients, there was roughly equal sex representation (45.9% female) with an average age of 72 years. A majority (56.4%) had precapillary PH, while one-third had confirmed alternative etiologies of precapillary PH, such as CTD-PAH or CTEPH. The high prevalence of precapillary PH among patients with CKD in the absence of other risk factors or associated conditions points toward a potentially more direct relationship between PH and CKD, rather than one linked primarily by associated conditions such as CTD. Prior studies have described similar demographics and hemodynamic findings. A retrospective study from O'Leary et al. looking at PH and CKD demonstrated similar average age (64.5 years old) in the CKD and precapillary PH subgroup, but a smaller proportion of patients (27%, 82/302) were male.[7] Baseline mPAP and PVR were notably higher in our cohort: 44 versus 35 mmHg and 7.2 versus 4.7 WU, respectively.[7] Of note, our study included only patients with fairly severe (Stage IV CKD or beyond) renal disease, while prior studies have included patients with more mild renal impairment.

The NO-sGC-cyclic guanosine monophosphate (cGMP) pathway plays an integral role in the control of pulmonary vascular tone, and NO synthesis is often depleted or altered in patients with PAH.[16–18] Furthermore, asymmetric dimethylarginine (ADMA), an endogenous NO-synthesis inhibitor, is elevated in patients with CKD and considered a uremic toxin. Importantly, ADMA is associated with impairment in endothelium-dependent vasodilation, as it effectively depletes NO activity and promotes vascular constriction and remodeling.[3,15] Whether external administration of NO in PH-CKD led to improvements in pulmonary hemodynamics was not previously known, and this is the first study to evaluate the hemodynamic response of patients with precapillary PH or Cpc-PH and CKD to iNO during RHC. In our cohort, there were significant decreases in both mPAP and PVR following iNO administration. These effects seem to further support the pathophysiologic importance of the NO pathway in PH-CKD.[3,15] The acute average absolute decrease in PVR (2.4 WU) and mPAP (6.0 mmHg) are comparable or exceed those decreases seen in major PAH therapy efficacy trials. For example, in a randomized placebo-controlled trial of sildenafil versus placebo in PAH by Galie et al., the mean changes with 40 mg dose of sildenafil were −1.8 WU (PVR) and 2.6 mmHg (mPAP).[19] Thus, the statistically significant improvements in hemodynamics seen in our cohort with iNO are likely clinically important as well.

It is important to note that iNO administration was associated with not only increased CO but also PAWP, suggesting that caution is warranted when considering NO pathway modulation in this population. While the reason(s) for the observed small but significant PAWP increase are unclear, one may speculate that it relates to left atrial stiffness, diastolic dysfunction, and the tenuous volume balance often seen in patients with significant renal dysfunction. Furthermore, patients' response to iNO may be influenced by the nature of the disease process(es) causing CKD (e.g., diabetes mellitus, hypertension, glomerular disease, etc.), which could be an informative area of future study.

Notably, survival among patients included in the study was poor. Patients had a median survival of only 3.1 years from RHC, emphasizing the poor prognosis associated with concomitant PH and CKD. There was no difference in survival between hemodynamic phenotypes of PH. These findings contrast with prior studies that have found worse survival among patients with CKD and Cpc-PH although our ability to detect differences in survival was limited by the small sample size.[20] Interestingly, 11% ($n = 4$) of the cohort met formal hemodynamic criteria for vasoresponsiveness, and the vasoresponder subgroup had excellent short-term prognosis. These findings suggest that vasoresponsiveness could be an important prognostic marker in PH associated with CKD.

Unlike the clear evidence of acute hemodynamic improvement with iNO during RHC, treatment with PAH-targeted therapies (several of which target the NO pathway) was not associated with significant benefit in the subset ($n = 14$) who were started on therapy. There were several potential reasons that may have contributed

to this lack of benefit. First, PAH therapy may not have a sustained effect on the pulmonary vasculature in this setting or may not be beneficial in the long-term management of patients with CKD and other comorbidities. Next, in this small, retrospective sample with incomplete follow-up data, we were likely underpowered to assess interval change. Additionally, the average level of complex, multisystem illness and morbidity in this population was high. Many of the patients in the treatment group were hospitalized at least once between the initial RHC and follow-up, with frequent therapy interruptions. Treatment strategies were also quite heterogeneous, reflective of current real-world clinical practice in this medically challenging population who have no approved treatment options or established standard of care. Finally, given that this was a retrospective study, there was no placebo group for direct comparison. Regardless of the reason(s) for lack of observed clinical benefit, our data suggests caution in use of iNO response during RHC to make PAH treatment decisions in PH-CKD without further prospective and ideally randomized studies. The results of the SIOVAC trial also highlight the limitation of using acute hemodynamic response to iNO to guide off-label use of PH therapy in non-Group 1 PH. The SIOVAC study assessed PDE-5i (sildenafil) efficacy in patients with corrected valvular disease and persistent PH, a cohort with similar risk factors for left-heart dysfunction as those with CKD. Despite slight improvement with acute vasoreactivity testing, sildenafil was ultimately associated with increased heart failure hospitalizations and other adverse outcomes, again emphasizing the need for caution when using off-label PAH therapy.[21]

LIMITATIONS

Our study had several limitations. These include the retrospective nature of the study, the small sample size, and referral bias since iNO was only administered during RHC per the preference of the referring provider. We also included a heterogeneous cohort of patients with PH and CKD who had alternative etiologies of PH and thus may not be clinically classified as Group 5 PH. There was also potential selection bias due to cohort determination based on RHC reports and interpretations that may have led to underestimation of Cpc-PH frequency. Additionally, the short-term survival difference we observed between vasoresponders and nonresponders may have been inflated by the small sample size in the former group and, therefore, should be interpreted with caution. Regarding the treatment cohort, there was a lack of systematic treatment algorithm (given that none currently exists in this population) and heterogenous timing of follow-up clinical and objective evaluations.

CONCLUSIONS

Among patients with PH and CKD with an elevated PVR, iNO was associated with significant improvement in pulmonary hemodynamics, specifically mPAP and PVR. Future studies to determine whether therapies targeting the NO pathway are beneficial in PH-CKD are warranted to provide more evidence-based treatment approaches for this complex and understudied patient population.

AUTHOR CONTRIBUTIONS

Kathryn T. del Valle and Hilary M. DuBrock participated in research design, manuscript preparation, and data preparation and analysis. Michael J. Krowka, Carrie A. Schinstock, Karl A. Nath, Charles D. Burger, Yogesh N. Reddy, Robert P. Frantz, and Y. S. Prakash participated in research design and critical manuscript review.

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CONFLICT OF INTEREST STATEMENT

HMD has received research funding from Bayer Pharmaceuticals and has served on advisory boards and received consulting fees from Janssen. The other authors declare no conflict of interest.

ETHICS STATEMENT

Research was approved by the Mayo Clinic institutional review board.

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