



The role of exercise right heart catheterization to guide pulmonary hypertension therapy in older adults

Susanna Mak¹  | Shimon Kolker² | Natasha R. Girdharry¹ |
Robert F. Bentley³ | Felipe H. Valle⁴ | Vikram Gurtu¹  | K. H. Mok¹ |
Jakov Moric¹ | John Thenganatt¹ | John T. Granton¹

¹Department of Medicine, Sinai Health/
University Health Network, University of
Toronto, Toronto, Canada

²Clalit Health, Tel Aviv, Israel

³Faculty of Kinesiology and Physical
Education, University of Toronto,
Toronto, Canada

⁴Hospital de Clinicas de Porto Alegre,
Porto Alegre, Brasil

Correspondence

Susanna Mak, Mount Sinai Hospital, 600
University Ave Rm 1603, Toronto, ON
M5G 1X5, Canada.

Email: Susanna.mak@sinaihealth.ca

Funding information

Ontario Research Foundation,
Grant/Award Number: RE 09089; Heart
and Stroke Foundation of Canada,
Grant/Award Number: GIA 18-0022220

Abstract

The spectrum of patients referred for suspected pulmonary arterial hypertension (PAH) includes a population with clinical features suggestive of pulmonary hypertension due to left heart disease (PH-LHD). Even after right heart catheterization (RHC) performed at rest, it can be a challenge to identify patients who will clearly benefit from PAH drug therapy. Therefore, the objective of this study was to evaluate the role of exercise RHC to influence decisions regarding prescription of PAH drug therapy in this population. A retrospective cohort study was conducted of older adults with risk factors for PH-LHD and suspected PH referred for exercise RHC. One year follow-up was conducted to record clinical outcomes, all changes in PAH drug therapy, and changes in patient-reported quality of life. The final cohort included 61 patients, mean age of 69 ± 10 ; 44% and 34% had a history of coronary artery disease and atrial fibrillation respectively. Exercise changed the proportional breakdown of hemodynamic diagnoses from 36% No PH, 44% PAH, and 20% PH-LHD at rest to 15% No PH, 36% PAH, and 49% PH-LHD. Although a significant proportion of patients were reclassified as PH-LHD, there was an overall increase in the proportion of patients receiving PAH drug therapy, particularly for those with PAH confirmed by exercise RHC. A total of 11 PAH drug prescriptions were employed before exercise RHC increasing to 24 after ($p = 0.002$). Patients receiving PAH therapy demonstrated significant improvement in self-reported quality of life. Exercise RHC appeared to influence selection of PAH drug therapy.

KEYWORDS

hemodynamics, treatment

Susanna Mak and Shimon Kolker contributed equally to the study.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *Pulmonary Circulation* published by John Wiley & Sons Ltd on behalf of Pulmonary Vascular Research Institute.

INTRODUCTION

Advances in the medical management of pulmonary arterial hypertension (PAH) have spurred broad referral of patients with suspected pulmonary hypertension (PH) to specialty programs providing diagnostic and treatment interventions. The contemporary spectrum of PAH patients includes many older individuals with a high prevalence of cardiovascular risk factors (CVRF).^{1,2} The challenge for clinicians is to identify patients that will benefit from appropriate PAH drug therapy versus those with PH due to left heart disease [PH-LHD, particularly heart failure with preserved ejection fraction (HFpEF)] for whom PAH drug therapies have not shown benefit and may cause harm.^{3,4}

Right heart catheterization (RHC) is the diagnostic gold standard for PH, defined as a mean pulmonary artery pressure (mPAP) >20 mmHg. PAH is differentiated hemodynamically from PH-LHD by a pulmonary artery wedge pressure (PAWP) ≤ or >15 mmHg respectively.⁵ However, a significant proportion of patients meeting the hemodynamic criteria for PAH have a clinical profile suggestive of HFpEF.^{1,2} Exercise stress during RHC may clarify the contributions of pulmonary vascular or left heart pathophysiology to PH. It has been demonstrated that, in select populations, resting PH diagnoses can be reclassified by exercise in approximately 40% of patients,^{6–8} however, the effect on clinical management is less clear.

Accordingly, we examined the effect of exercise RHC within our PH program on decisions to implement or modify PAH drug therapy for up to 1 year amongst older patients with a high prevalence of CVRF.

METHODS

We conducted a retrospective cohort study of consecutive patients undergoing RHC with the systematic addition of exercise, who participated prospectively in a clinical and hemodynamic registry maintained at our center.⁶ Patients also completed questionnaires measuring quality of life at the time of exercise RHC, and 1-year follow-up was conducted to repeat questionnaires if possible and record clinical outcomes including death, transplant, or hospitalization.

For this analysis, patients referred by our center's PH program were included if they were >50 years of age, and had one or more CVRF (BMI ≥ 30 kg/m², history of hypertension treated with ≥1 medication, hypercholesterolemia treated with at least one medication, diabetes mellitus treated with oral hypoglycemic agents or insulin, or a history of coronary artery disease). Inclusion criteria

also mandated an echocardiogram demonstrating normal left ventricular ejection fraction and suspected PH based on the peak velocity of the tricuspid regurgitation jet >2.8 m/s, or previous RHC documenting PH. Patients were excluded if they were recipients of a heart transplant or left ventricular assist device, had a history of pericardial disease, recent acute coronary syndrome, or evidence of structural heart disease with more than moderate valvular regurgitation or stenosis. Patients with hypoxic pulmonary disease or a history of venous thromboembolic disease (suspected Group 3 or 4 PH) were also excluded.

As part of registry practices, a case report form was completed at the time of RHC. Information collected included demographics and all clinical data captured as part of standard practice in the PH program. Clinical information included risk factors for PH, CVRF, and complete medication history. Both the Short Form 36 (SF36) Quality of Life questionnaire and the Medical Research Council (MRC) Breathlessness Scale were administered.

Catheterization procedures

Our methods for resting supine RHC and exercise on a semi-upright ergometer have been reported previously.^{6,9,10} Briefly, supine resting RHC was performed and pressures were sampled from the right atrium, right ventricle, and pulmonary artery. The balloon-tip was intermittently inflated for measurement of the PAWP. Blood sampling for mixed venous oxygen saturation and thermodilution cardiac output (TDCO) was measured intermittently. For exercise testing, patients were transferred to a tiltable cycle ergometer and performed semi-upright exercise at 1 or 2 timed constant work-rate stages. Each exercise stage lasted for 5 min and TDCO was obtained in triplicate within 10% after the second minute of exercise. Selection of first/second work rates were based on the MRC breathlessness scale; scores of 4 or higher—15/25 watts (W), scores of 3 or less—25/40W for women and 40/70 W for men.⁶

Procedures for hemodynamic analysis have been published by our lab.^{6,9,10} Hemodynamics reported include heart rate (HR), systemic blood pressure, mean right atrial pressure (mRAP), systolic/diastolic/mean PAP (PASP/PADP/mPAP), TDCO, and mPAWP. Supine resting hemodynamic classifications were reported as per the World Symposium for Pulmonary Hypertension (WSPH) definitions for PH (mPAP > 20 mmHg), PAH (mPAP > 20 mmHg, PAWP ≤ 15 mmHg, PVR ≥ 3 WU) and PH-LHD (mPAP >20 mmHg, PAWP > 15 mmHg).⁵ Exercise hemodynamic classifications and discrimination between normal and abnormal were based on pressure-flow slopes derived from healthy, self-reported non-

dyspneic volunteers as reported by our laboratory previously.⁶ Exercise PH was defined by $mPAP/CO > 3$ WU,¹¹ and subclassified as Exercise PH-LHD if change in PAWP per change in CO with exercise ($\Delta PAWP/\Delta CO$) > 2 mmHg/L/min,^{9,12} and Exercise PAH if the $\Delta PAWP/\Delta CO$ was ≤ 2 mmHg/L/min.

Follow-up procedures

Patients were contacted at 1 year following exercise RHC and the SF36 questionnaire was repeated if possible. Vital status and hospital admissions including dates and diagnoses were corroborated by hospital records.

Retrospective evaluation of PAH therapy

A chart review was conducted to record all ambulatory visits to the PH clinic up to 1 year after the exercise RHC. All medication changes made during this period were recorded. Results of follow-up tests were also recorded from the patients' medical records and the treating physician reports.

Ethical approval

The prospective hemodynamic and clinical registry was approved by Mount Sinai Hospital's research ethics board (REB no. 16-0217-E) and all patients gave written informed consent. Approval was also obtained for retrospective chart review of ambulatory clinic activity during follow-up.

Data analysis

Continuous data was presented as mean \pm standard deviation (SD) if normally distributed and as median (interquartile range [IQR]) if not normally distributed. Dichotomous variables were expressed as percentages. One of three diagnoses could be assigned: No PH, PAH, or PH-LHD. In the supine position, an initial hemodynamic diagnosis was assigned; however, the final diagnosis was assigned after exercise RHC. If patients were unable to exercise, or exercise results were equivocal, they retained the resting diagnosis. Rest and exercise hemodynamic measurements were evaluated by a two-way repeated-measures analysis of variance, with rest/exercise as the repeated factor and diagnosis as the second factor. Post hoc pairwise comparisons were performed with a Bonferroni correction. The effect of exercise RHC to change hemodynamic PH classification

pre and postexercise RHC was evaluated with McNemar's test. Data was available with respect to changes in PAH drug therapy on a portion of the sample. The effect of exercise RHC to affect the proportion on monotherapy and dual therapy before and after exercise RHC was also evaluated with McNemar's test. SF36 scores for specific domains as well as the overall quality of life were also compared before and 1 year after exercise RHC was assessed in the full cohort with a Wilcoxon Signed Rank Test. $p < 0.05$ was required for statistical significance.

RESULTS

Patient characteristics

Between July 2017 and June 2020, 61 patients were identified who met inclusion and exclusion criteria. Demographic and clinical characteristics are presented in Table 1. Patients had a mean age of 69 ± 10 and 56% were

TABLE 1 Patient characteristics, $n = 61$

Age (y)	69 \pm 10
Women n (%)	34 (56%)
Body surface area (m ²)	1.92 \pm 0.25
Body mass index (BMI) (kg/m ²)	28.7 \pm 5.2
BMI > 25 and ≥ 30 kg/m ²	21 (34%) and 25 (41%)
Diabetes mellitus n (%)	19 (31%)
Hypertension	47 (77%)
Dyslipidemia	36 (59%)
History of atrial fibrillation	21 (34%)
History of coronary artery disease	27 (44%)
Asthma or chronic obstructive lung disease	20 (33%)
Connective tissue disease	4 (7%)
Angiotensin-converting enzyme inhibitors	34 (56%)
Beta-adrenergic receptor blockers	37 (61%)
Calcium channel blockers	21 (34%)
Acetylsalicylic acid	28 (46%)
Anticoagulant	19 (31%)
Loop diuretic	29 (48%)
Thiazide diuretic	7 (11%)
Spironolactone	15 (25%)
HMG-CoA reductase inhibitors	36 (59%)
NT-pro BNP pg/ml	131 \pm 235

	All patients <i>n</i> = 61	No PH <i>n</i> = 22	PAH <i>n</i> = 27	PH-LHD <i>n</i> = 12	<i>p</i> value
HR min ⁻¹	67 ± 11	65 ± 11	67 ± 10	69 ± 12	0.504
MAP (mmHg)	95 ± 17	91 ± 12	100 ± 20	90 ± 15	0.072
SVi (mlm ⁻²)	38 ± 10	43 ± 10	35 ± 9*	35 ± 8	0.012
CI (Lmin ⁻¹ m ⁻²)	2.5 ± 0.6	2.7 ± 0.6	2.3 ± 0.6	2.4 ± 0.7	0.068
mRAP (mmHg)	7 ± 4	4 ± 3	7 ± 3*	11 ± 3* [†]	<0.001
SPAP	47 ± 22	25 ± 5	58 ± 20*	61 ± 16*	<0.001
DPAP	15 ± 8	7 ± 3	19 ± 6*	21 ± 6*	<0.001
mPAP	28 ± 13	15 ± 3	34 ± 10*	38 ± 9*	<0.001
mPAWP	12 ± 5	8 ± 3	12 ± 4*	19 ± 4* [†]	<0.001
PVR (WU)	3.9 ± 3.4	1.5 ± 0.9	5.7 ± 3.9*	4.3 ± 2.6*	<0.001
PAC	3.1 ± 2.0	4.8 ± 1.9	2.2 ± 1.4*	2.0 ± 1.1*	<0.001

Abbreviations: CI, cardiac index; DPAP, diastolic pulmonary artery pressure; HR, heart rate; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; mPAWP, mean pulmonary artery wedge pressure; mRAP, mean right atrial pressure; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SPAP, systolic pulmonary artery pressure; SVi, stroke volume index.

**p* < 0.05 versus no PH.

[†]*p* < 0.05 versus PAH.

female. The study cohort exhibited a high burden of CVRF. Approximately three-quarters of the population were overweight or obese and the prevalence of diabetes and hypertension was 31% and 77%, respectively. Moreover, 44% had a history of coronary artery disease and 34% had a history of prior or current atrial fibrillation. Before RHC with exercise, 19 patients (31%) were known to have PAH based on a previous resting RHC. The remainder of the population was referred for suspected PH as outlined by the inclusion criteria. The median MRC score was 4^{3,4} and the median work rate for the first stage was 25 W.^{15,25} The mixed venous oxygen saturation declined to a median value of 41% with a range of 14.5%–58.5% and 24 patients proceeded to a second stage.

Exercise reclassification of hemodynamic diagnoses

Hemodynamics measured at baseline in the supine position are presented in Table 2. At rest, classifications were: No PH = 22 (36%) and PH = 39 (64%). Further hemodynamic classifications of the PH group were: PAH = 27 (44%) and PH-LHD = 12 (20%). Between the groups with resting PH, PH-LHD patients exhibited higher mRAP and mPAWP than PAH, but otherwise no differences in HR, TDCO, or PAPs. The mPAWP was

19 ± 4 mmHg in the PH-LHD group and 12 ± 4 mmHg in the PAH group. In the PH-LHD group, 9 or 12 patients demonstrated combined pre- and postcapillary PH based on PVR > 3WU.

The effect of exercise to alter rest hemodynamic classifications are presented in Figures 1 and 2, and hemodynamics grouped by final classification after exercise are included in Table 3. Among patients with No PH at rest (*n* = 22), nine remained classified as No PH, four were reclassified as PAH, and nine were reclassified as PH-LHD. Among patients classified as PAH at rest (*n* = 27), 14 remained classified as PAH, 11 were reclassified as PH-LHD, and 2 did not complete exercise. Among patients classified as PH-LHD at rest (*n* = 12), nine remained classified as PH-LHD, two were reclassified as PAH, and one did not complete exercise. Interestingly, five patients with PH at rest (4 PAH and 1 PH-LHD) did not meet the exercise mPAP/CO criteria for PH. In addition, three patients overall did not complete the exercise portion (2 PAH and 1 PH-LHD). The reasons exercise was not performed included orthopedic restrictions to cycle ergometry (two patients) and the development of chest pain during the resting RHC (one patient). These eight patients retained their resting hemodynamic classification. Overall, after exercise RHC, final hemodynamic classifications were: No PH = 9 (15%), PAH = 22 (36%), and PH-LHD = 30 (49%). The number of patients classified as No PH decreased

TABLE 2 Baseline supine hemodynamic measurements by resting PH classification

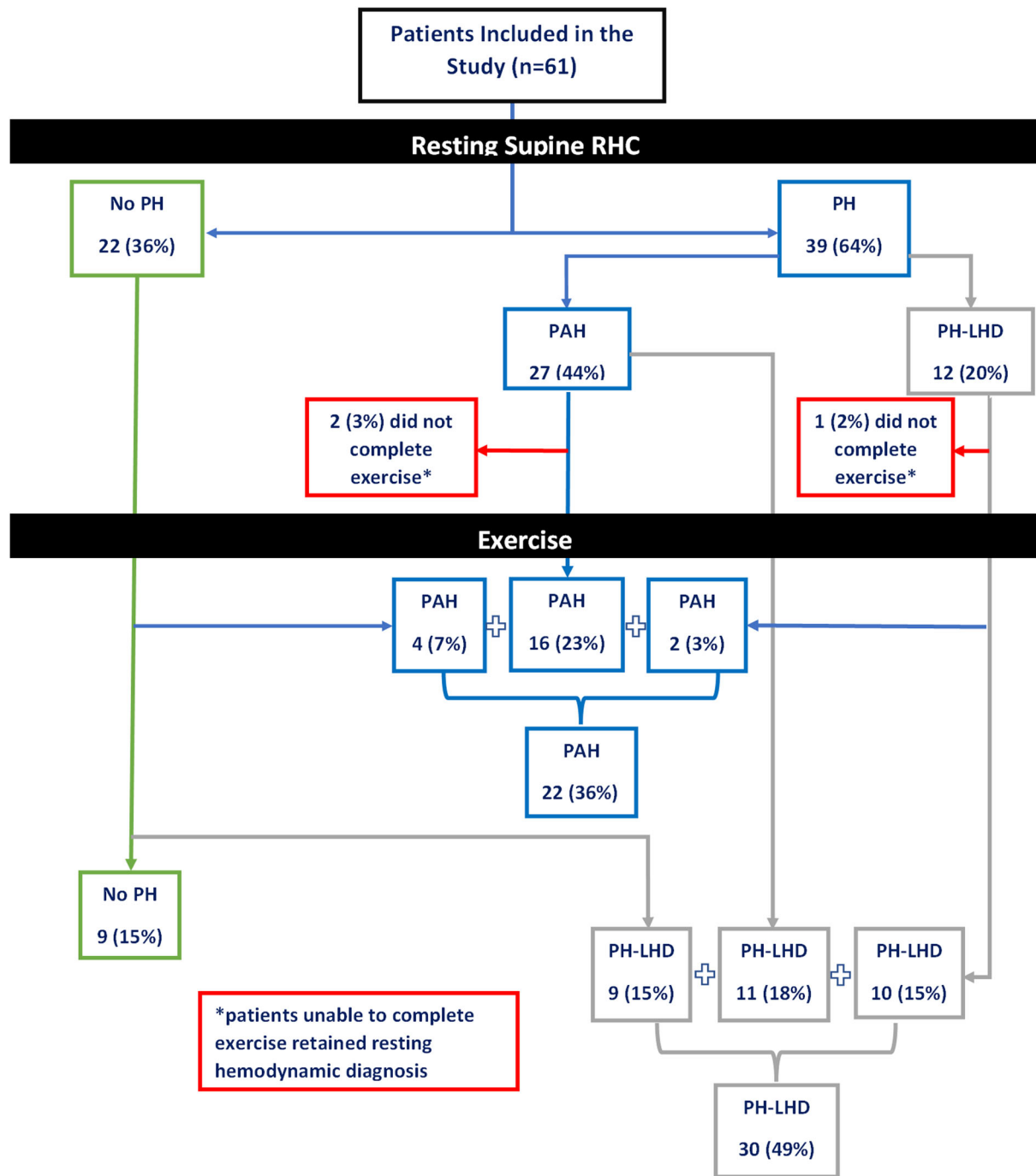


FIGURE 1 Flow diagram resting hemodynamic classification and reclassification by exercise RHC. PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; PH-LHD, pulmonary hypertension due to left heart disease; RHC, right heart catheterization.

from 22 to 9 between rest and exercise; in other words, the proportion of the total population classified as having some form of PH increased from 64% to 85% ($p = 0.0009$). The relative proportions of patients with PAH versus PH-LHD also shifted significantly between rest and exercise; after rest RHC, the proportion of PAH versus PH-LHD was 44% versus 20%, but after exercise RHC this changed to 36% versus 49% ($p = 0.01$).

Clinical events and PAH therapy

In the cohort, there were nine hospitalizations (6 for congestive heart failure) and four deaths in follow-up (final diagnoses 3 PAH and 1 PH-LHD). Twenty-six patients did not receive longitudinal follow-up in the PH clinic after exercise RHC; 77% of those without follow-up either had a final diagnosis of No PH ($n = 6$) or PH-LHD ($n = 14$).

In total, after exercise RHC, 35 patients had follow-up over 1 year in the PH clinic (final diagnoses 3 No PH, 16 PAH, and 16 PH-LHD), including all patients who were receiving PAH therapy and/or were known to have PH based on a previous resting RHC. Table 4 and Figure 3 summarize the medication changes made in the first year of follow-up. The median number of clinic visits for these patients over the first year was five visits. Before exercise RHC, 10 patients were receiving therapy (9 PAH and 1 PH-LHD) and 25 were not (3 Normal, 7 PAH, and 15 PH-

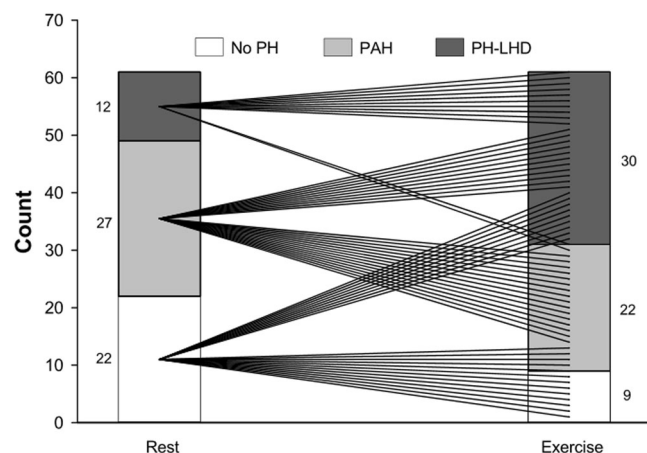


FIGURE 2 Summary of rest to exercise hemodynamic classification. PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; PH-LHD, pulmonary hypertension due to left heart disease.

LHD). Among the 10 treated patients, nine were treated with a single agent and one was treated with two agents. One-year after exercise RHC, 18 patients were receiving therapy (13 PAH and 5 PH-LHD) and 17 were not (3 No PH, 3 PAH, and 11 PH-LHD) ($p = 0.05$ vs. pre-exercise RHC) (Figure 4). A total of 11 PAH drug prescriptions were employed before exercise RHC increasing to 24 PAH drug prescriptions after ($p = 0.002$). The most significant change was an increase in the number of prescriptions for endothelin receptor antagonists.

Whether exercise confirmed or changed the hemodynamic classifications and subsequent changes in PAH therapy are illustrated in Table 5. Sixteen patients with a final diagnosis of PAH received follow-up. Eight had resting PH-LHD for whom exercise confirmed the diagnosis (1 remained on monotherapy and 2 were started on monotherapy) while for the remaining eight exercise changed the diagnosis to PH-LHD (2 were started on monotherapy). Overall, at 1 year, 5 of the 16 PH-LHD patients were receiving PH therapy, all monotherapy. Sixteen patients with a final diagnosis of PAH received follow-up. Fifteen had resting PAH for whom exercise confirmed the diagnosis (7 remained on monotherapy, 6 were escalated mostly to dual therapy, and 2 had de-escalation of therapy), while for one patient, exercise had changed their diagnosis to PAH (and started on monotherapy). Overall at 1 year, 13 of the 16 PAH patients were receiving PH therapy. Of note, confirmation of the PAH diagnosis led to escalation of therapy for 38% of this group.

	All completing exercise N = 58	No PH N = 9	PAH N = 20	PH-LHD N = 29
HR min ⁻¹	95 ± 15	88 ± 13	101 ± 18	95 ± 14
MAP (mmHg)	101 ± 21	106 ± 15	99 ± 13	100 ± 26
CI (Lmin ⁻¹ m ⁻²)	3.9 ± 1.2	4.8 ± 1.7	3.7 ± 1.0	3.7 ± 0.1.0
mRAP (mmHg)	11 ± 7	6 ± 6	13 ± 7*	13 ± 6*
SPAP	64 ± 27	45 ± 24	82 ± 33	63 ± 16
DPAP	25 ± 10	15 ± 10	31 ± 10*	27 ± 7*
mPAP	43 ± 16	28 ± 13	52 ± 19*	44 ± 10*
mPAWP	18 ± 9	11 ± 5	13 ± 6	25 ± 6*†
PVR (WU)	3.8 ± 3.6	2.4 ± 3.0	6.5 ± 5.1*	2.9 ± 1.8†
PAC	2.7 ± 1.7	4.3 ± 2.0	2.3 ± 2.1	2.3 ± 0.9

Abbreviations: CI, cardiac index; DPAP, diastolic pulmonary artery pressure; HR, heart rate; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; mPAWP, mean pulmonary artery wedge pressure; mRAP, mean right atrial pressure; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SPAP, systolic pulmonary artery pressure.

* $p < 0.05$ versus no PH.

† $p < 0.05$ versus PAH.

TABLE 3 Exercise hemodynamic measurements based on exercise PH classifications

TABLE 4 Changes in medications among 35 patients receiving follow-up in PH clinic

Therapy	Pre-exercise RHC	Postexercise RHC	p value
No therapy n (%)	25 (71)	17 (49)	0.05
Single-agent therapy			
PDE5 inhibitor	8 (23)	9 (26)	
ET receptor antagonist	1 (3)	4 (11)	
Total	9 (26)	13 (37)	0.31
Combination therapy			
PDE5 inhibitor + ET receptor antagonist	1 (3)	4 (11)	
Other combination	0	1 (3)	
Total	1 (3)	5 (14)	0.09
PAH prescriptions			
PDE5 Inhibitor	9 (26)	14 (40)	0.21
ET receptor antagonists	2 (6)	9 (26)	0.02
Other agent	0	1 (3)	
Total	11 (31)	24 (69)	0.002

Note: Data presented as n (%).

Abbreviations: ET, endothelin; PDE5, phosphodiesterase type 5; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization.

Changes in quality of life

Some follow-up measurements could not be obtained as the follow-up period overlapped with the COVID 19 pandemic, which restricted in person clinic visits. One-year follow-up SF 36 scores were available for 12/18 patients receiving PAH treatment (final diagnoses 8 PAH and 4 PH-LHD) and 9/17 patients not receiving treatment (final diagnoses 1 No PH, 3 PAH, and 5 PH-LHD).

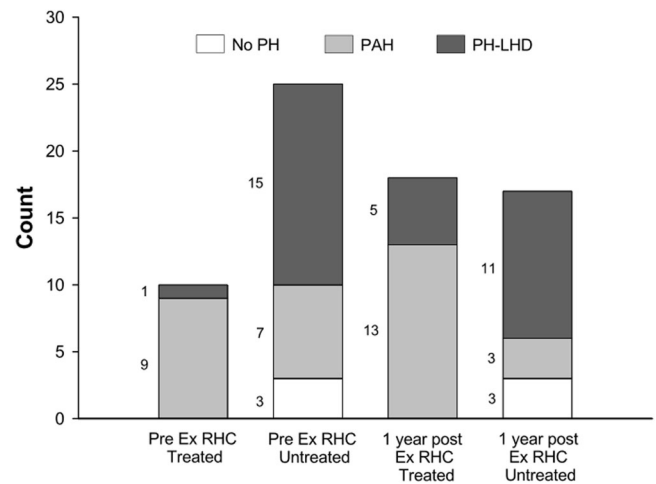


FIGURE 4 Proportion of patients treated and untreated at baseline and 1-year follow-up and final exercise hemodynamic classification. PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension due to left heart disease; RHC, right heart catheterization.

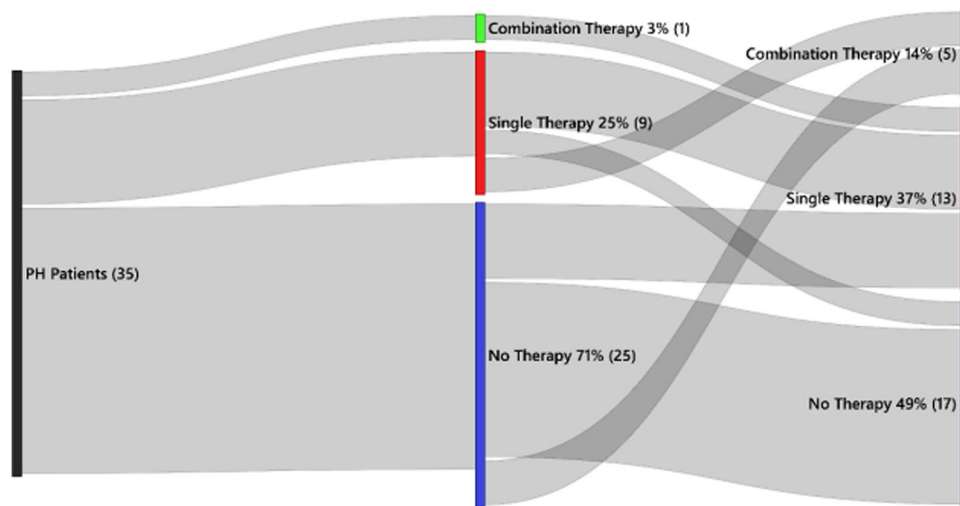


FIGURE 3 Changes in PAH drug prescription in 35 patients during 1-year follow-up in PH clinic. PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

TABLE 5 Hemodynamic classifications and changes in treatment (Rx) at 1 year

Final diagnosis (Expected PH Rx)	Resting diagnosis	Diagnosis changed or confirmed	PH Rx changed at 1 year	Description
No PH ($n = 3$) (NoRx)	No PH ($n = 3$)	Confirmed	No ($n = 3$)	NoRx Baseline or 1 year
PH-LHD ($n = 16$) (NoRx or monoRx)	No PH ($n = 3$)	Changed	No ($n = 3$)	NoRx Baseline or 1 year
	PH-LHD ($n = 8$)	Confirmed	Yes ($n = 2$)	2 escalated from NoRx to monoRx
				No ($n = 6$)
PAH ($n = 5$)	PAH ($n = 5$)	Changed	Yes ($n = 2$)	2 escalated from NoRx to monoRx
			No ($n = 3$)	3 NoRx Baseline or 1 year
PAH ($n = 16$) (Mono or DualRx)	PH-LHD ($n = 1$)	Changed	Yes ($n = 1$)	1 escalated from NoRx to monoRx
	PAH ($n = 15$)	Confirmed	Yes ($n = 8$)	6 escalated Rx
			No ($n = 7$)	5 to dualRx or more 2 from monoRx 3 from NoRx 1 from NoRx to monoRx 7 Rx unchanged 5 remained on monoRx 2 No Rx Baseline or 1 year

Abbreviations: PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension due to left heart disease.

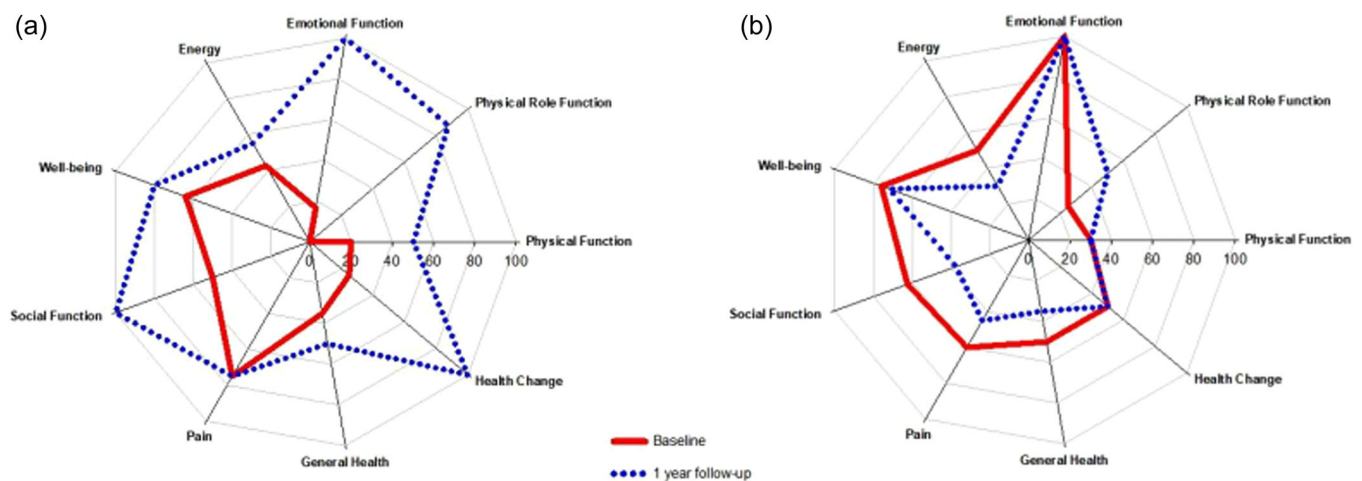


FIGURE 5 Baseline and 1-year SF36 results according to treatment status: (a) Patients receiving PAH therapy, (b) patients not receiving PAH therapy. PAH, pulmonary arterial hypertension; SF36, Short Form-36.

Figure 5 includes radar plots to examine changes in quality of life for patients with 1-year follow-up according to treatment status. In our cohort of older adults with risk factors for cardiovascular disease undergoing exercise RHC, patients receiving PH therapy demonstrated

significant improvements for domains reflecting physical role function, health change, well-being, social and emotional function. Patients who were not receiving PAH therapy did not demonstrate significant changes in any domains of quality of life.

DISCUSSION

We studied the effect of exercise RHC to support selection of PAH drug therapy among older patients with a high prevalence of CVRF referred to our PH program for confirmed or suspected PH. We observed several outcomes for this patient population, including initiation, escalation, as well as withdrawal of PAH therapy. Overall, there was a net increase in the number of prescriptions for PAH-specific medications and improvements in self-reported quality of life particularly for patients receiving treatment.

The experience of both registries¹ and clinical trials² has shown that patients referred to expert PAH centers are often older, with a higher prevalence of CVRF than traditionally considered. Patients with a high burden of CVRF were excluded from landmark studies establishing the efficacy of dual therapy with PDE5i and ET antagonists,² leading to uncertainty regarding both the diagnostic and therapeutic strategy for this population. The current study confirmed this experience in our PH program, and we identified a population with a mean age of approximately 70 years, with >90% having at least two CVRF. We further excluded patients with suspected WHO group 3 or 4 PH. Our inclusion criteria mandated a high likelihood of PH based on previous investigations, to exclude patients referred for dyspnea of unknown origin likely to have normal resting hemodynamics. Almost 1/3 of the population had previous documentation of PH by RHC, yet only 50% of these were treated, primarily with single-agent PAH therapy, reflecting the uncertainty of experienced clinicians for prescribing dual PAH therapy in this population.

An assumption made in this study was that exercise RHC would improve the precision of PH diagnosis. It is important to acknowledge that fully standardized recommendations for either the methods or interpretation of data are lacking.^{13,14} The clinical indication for patients referred in this study was to identify specific pathophysiology underlying probable PH. As such, 85% of our population had abnormal rest or exercise hemodynamics, a higher proportion than studies of patients with dyspnea of unknown origin with and without risk factors for latent PAH or PH-LHD.^{7,8,15} Given the older age, comorbidities and symptom-burden of this population, the exercise protocol employed modest work-rates, with over half of the cohort unable to progress beyond the first exercise work rate. As such, classification of physiology were not based on single value thresholds, which may vary based on the body position.¹¹ Pressure-flow relationships were employed, which may be more sensitive for detection of abnormal responses¹³ and also allows interpretation of both PAP

and PAWP as well as their interrelationship. In this population, exercise unmasked PAH or PH-LHD in 59% of patients without PH at rest. Importantly, among this older population, exercise also shifted the dominant PH diagnosis from PAH to PH-LHD, ultimately identified in almost half the cohort.

The relationship between exercise RHC and selection of PAH drug therapies was complex. Variations in referral practice with respect to timing for exercise RHC were evident; some patients were referred at the time of initial diagnostic RHC but others referred in ongoing follow-up. As noted, a pre-existing diagnosis of PH was available for approximately 1/3 of the cohort, however, less than 50% of these patients were receiving any therapy. Although similar patients have been shown to benefit,^{16,17} our data is consistent with hesitation to initiate PAH drug therapy in this older population^{18,19} who would have been excluded from clinical trials based on their burden of CVRF. Further, the selection of a single agent strategy, primarily PDE5i, likely reflects the concern for harm with ET antagonists in a population that may in actuality have PH-LHD.^{3,4} The substantial reclassification of our cohort to PH-LHD would substantiate this concern of clinicians. Approximately 40% of patients were discharged from the PH program after exercise RHC, the majority of whom were demonstrated to have either No PH or PH-LHD. Interestingly, despite the preponderance of PH-LHD and the small number of patients withdrawn from PAH therapy, more prescriptions for PAH drug therapy were issued after exercise RHC. As important as uncovering PH-LHD, confirmation of PAH (and definitively ruling out PH-LHD) by exercise RHC appeared to increase confidence for clinicians to prescribe PAH-specific therapy and escalate from single agent to dual therapy, particularly with the addition of ET antagonists.

Although exercise RHC appeared to exert some influence on decisions regarding PAH therapy, there were patients who received therapy despite a final diagnosis of PH-LHD and similarly patients with a final diagnosis of PAH were either not offered therapy or perhaps did not tolerate therapy. Although our study was not powered to establish a connection between exercise RHC and outcomes, we did observe clear improvements in quality of life at 1-year follow-up for patients receiving treatment. This was a highly selected population for whom it seems plausible that exercise RHC may have assisted in identifying patients most likely to benefit from PAH therapy. Among patients with a final diagnosis of PH-LHD, whether decisions to withdraw or withhold PAH therapy reduced harm is not clear from our study, although as a group quality of life was neither improved nor diminished.

Several limitations merit discussion. This was a single-center experience and it would be useful to test a strategy of provocative RHC either in a prospective and randomized and/or a multicenter fashion. The strategy for selection of PAH drug therapy was not uniform; a portion of patients was referred for exercise at the time of initial RHC, while others were referred after initiation of single-agent PAH therapy. We did not have a complete follow-up of the full cohort. The criteria by which to define abnormal exercise PAWP responses are still in evolution,^{13,14} and an infusion of intravenous saline is a viable alternative to elicit evidence of left heart disease;²⁰ however, exercise may be preferable to stress the pulmonary vasculature in addition.²¹

There remain several unresolved issues with respect to the clinical utility of exercise RHC. Our experience validates the notion that, for many patients with overlapping risk factors for WHO group 1 and 2 diseases, resting hemodynamics do not provide sufficient resolution to distinguish between the different subtypes of PH. Exercise RHC appeared to influence the selection of PAH drug therapy both in the case where exercise confirmed the diagnosis as well as when exercise changed the diagnosis. Further study is required to assess whether patient outcomes are improved.

AUTHOR CONTRIBUTIONS

Susanna Mak, Shimon Kolker, and John T. Granton: Concept and study design. Susanna Mak, Shimon Kolker, Natasha R. Girdharry, Robert F. Bentley, Felipe H. Valle, Vikram Gurtu, and K. H. Mok: Data acquisition and analysis. Susanna Mak, Shimon Kolker, Jakov Moric, John Thenganatt, and John T. Granton: Drafted and revised manuscript. All authors reviewed and approved manuscript.

ACKNOWLEDGMENTS

The study was funded by Heart and Stroke Foundation of Canada Grant-in-Aid and the Ontario Research Fund, Research Excellence.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Institutional REB #16-0217-E.

GUARANTOR

Dr. Mak is the guarantor of the data presented in this manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Susanna Mak  <http://orcid.org/0000-0003-2193-602X>

Vikram Gurtu  <http://orcid.org/0000-0003-3517-592X>

REFERENCES

1. Frost AE, Badesch DB, Barst RJ, Benza RL, Elliott CG, Farber HW, Krichman A, Liou TG, Raskob GE, Wason P, Feldkircher K, Turner M, McGoon MD. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US contemporary registries. *Chest*. 2011;139(1):128–37. <https://doi.org/10.1378/chest.10-0075>
2. Galie N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*. 2015;373(9):834–44. <https://doi.org/10.1056/nejmoa1413687>
3. Hoendermis ES, Liu LC, Hummel, van der Meer P, de Boer RA, Berger RM, van Veldhuisen DJ, Voors AAYM. Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial. *Eur Heart J*. 2015;36(38):2565–73. <https://doi.org/10.1093/eurheartj/ehv336>
4. Vachiéry JL, Delcroix M, Al-Hiti, Efficace M, Hutyra M, Lack G, Papadakis K, Rubin LJH. Macitentan in pulmonary hypertension due to left ventricular dysfunction. *Eur Respir J*. 2018;51(2):1701886. <https://doi.org/10.1183/13993003.01886-2017>
5. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1). <https://doi.org/10.1183/13993003.01913-2018>
6. Bentley RF, Barker M, Esfandiari S, Wright SP, Valle FH, Granton JT, Mak S. Normal and abnormal relationships of pulmonary artery to wedge pressure during exercise. *J Am Heart Assoc*. 2020;9(22):16339. <https://doi.org/10.1161/JAHA.120.016339>
7. Borlaug BA, Nishimura RA, Sorajja P, Lam CSP, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Hear Fail*. 2010;3(5):588–95. <https://doi.org/10.1161/CIRCHEARTFAILURE.109.930701>
8. Ho JE, Zern EK, Lau, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Farrell R, Sbarbaro JA, Schoenike MW, Houstis NE, Baggish AL, Shah RV, Naylor M, Malhotra R, Lewis GDES. Exercise pulmonary hypertension predicts clinical outcomes in patients with dyspnea on effort. *J Am Coll Cardiol*. 2020;75(1):17–26. <https://doi.org/10.1016/j.jacc.2019.10.048>
9. Esfandiari S, Wright SP, Goodman JM, Sasson Z, Mak S. Pulmonary artery wedge pressure relative to exercise work rate in older men and women. *Med Sci Sport Exerc*. 2017;49(7):1297–1304. <https://doi.org/10.1249/MSS.0000000000001227>
10. Wright SP, Esfandiari S, Gray T, Fuchs FC, Chelvanathan A, Chan W, Sasson Z, Granton JT, Goodman JM, Mak S. The pulmonary artery wedge pressure response to sustained exercise is time-variant in healthy adults. *Heart*. 2016;102(6):438–43. <https://doi.org/10.1136/heartjnl-2015-308592>

11. Kovacs G, Herve P, Barbera JA, et al. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J*. 2017;50(5):1700578. <https://doi.org/10.1183/13993003.00578-2017>
12. Lewis GD, Bossone E, Naeije R, et al. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation*. 2013;128:1470–79. <https://doi.org/10.1161/CIRCULATIONAHA.112.000667>
13. Vachiery JL, Tedford RJ, Rosenkranz S, et al. Pulmonary hypertension due to left heart disease. *Eur Respir J*. 2019;53:1801897. <https://doi.org/10.1183/13993003.01897-2018>
14. Baratto C, Caravita S, Soranna D, et al. Current limitations of invasive exercise hemodynamics for the diagnosis of heart failure with preserved ejection fraction. *Circ Heart Failure*. 2021;14:e007555. <https://doi.org/10.1161/CIRCHEARTFAILURE.120.007555>
15. Condliffe R. Unmasking hidden disease: exercise pulmonary haemodynamics in systemic sclerosis. *Eur Respir J*. 2017;50:1700885. <https://doi.org/10.1183/13993003.00885-2017>
16. Grünig E, Huscher D, Pittrow D, Vizza D, Hoepfer MM. Pulmonary hypertension due to lung disease: results from COMPERA. *Eur Respir J*. 2015;46(suppl 59):OA5000. <https://doi.org/10.1183/13993003.CONGRESS-2015.OA5000>
17. McLaughlin VV, Vachiery JL, Oudiz RJ, et al. Patients with pulmonary arterial hypertension with and without cardiovascular risk factors: results from the AMBITION trial. *J Heart Lung Transplant*. 2019;38(12):1286–95. <https://doi.org/10.1016/J.HEALUN.2019.09.010J>
18. Hoepfer MM, Huscher D, Ghofrani, Delcroix M, Distler O, Schweiger C, Grünig E, Staehler G, Rosenkranz S, Halank M, Held M, Grohé C, Lange TJ, Behr J, Klose H, Wilkens H, Filusch A, Germann M, Ewert R, Seyfarth HJ, Olsson KM, Opitz CF, Gaine SP, Vizza CD, Vonk-Noordegraaf A, Kaemmerer H, Gibbs JS, Pittrow DHA. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. *Int J Cardiol*. 2013;168(2):871–80.
19. Ling Y, Johnson MK, Kiely, Condliffe R, Elliot CA, Gibbs JS, Howard LS, Pepke-Zaba J, Sheares KK, Corris PA, Fisher AJ, Lordan JL, Gaine S, Coghlan JG, Wort SJ, Gatzoulis MA, Peacock AJDG. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. *Am J Respir Crit Care Med*. 2012;186(8):790–6.
20. D'Alto M, Badesch D, Bossone, Borlaug BA, Brittain E, Humbert M, Naeije RE. A fluid challenge test for the diagnosis of occult heart failure. *Chest*. 2021;159(2):791–7. <https://doi.org/10.1016/j.chest.2020.08.019>
21. Maron BA, Kovacs G, Vaidya, Bhatt DL, Nishimura RA, Mak S, Guazzi M, Tedford RJA. Cardiopulmonary hemodynamics in pulmonary hypertension and heart failure: JACC review topic of the week. *J Am Coll Cardiol*. 2020;76(22):2671–81. <https://doi.org/10.1016/j.jacc.2020.10.007>

How to cite this article: Mak S, Kolker S, Girdharry NR, Bentley RF, Valle FH, Gurtu V, Mok KH, Moric J, Thenganatt J, Granton JT. The role of exercise right heart catheterization to guide pulmonary hypertension therapy in older adults. *Pulmonary Circulation*. 2022;12:e12103. <https://doi.org/10.1002/pul2.12103>