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ORIGINAL RESEARCH

# iCPET Calculator: A Web-Based Application to Standardize the Calculation of Alpha Distensibility in Patients With Pulmonary Arterial Hypertension

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**BACKGROUND:** Pulmonary vascular distensibility associates with right ventricular function and clinical outcomes in patients with unexplained dyspnea and pulmonary hypertension. Alpha distensibility coefficient is determined from a nonlinear fit to multipoint pressure-flow plots. Study aims were to (1) create and test a user-friendly tool to standardize analysis of exercise hemodynamics including distensibility, and (2) investigate changes in distensibility following treatment in patients with pulmonary arterial hypertension.

**METHODS AND RESULTS:** Participants with an exercise right heart catherization were retrospectively identified from the University of Arizona Pulmonary Hypertension (UA PH) registry and split into a pulmonary arterial hypertension group, a comparator group, and a control group. Right ventricular function was quantified using the coupling ratio and diastolic stiffness. Prototypes of the invasive cardiopulmonary exercise testing (iCPET) calculator were developed using Matlab, Python, and RShiny to analyze exercise hemodynamics and alpha distensibility coefficient, α (%/mm Hg) from multipoint pressure flow plots. Interclass correlation coefficients were calculated for interplatform and interobserver variability in alpha. No significant bias in the intraplatform (Matlab versus RShiny; intraclass correlation coefficient: 0.996) or interobserver (intraclass correlation coefficient: 0.982) comparison of alpha values. Afterload significantly decreased ($P$<0.05) with no change in alpha distensibility in the pulmonary arterial hypertension group at follow-up. The comparator group had no change in pressure, resistance or alpha distensibility. There were no significant changes in RV diastolic stiffness at follow-up.

**CONCLUSIONS:** The interactive user interface in the iCPET calculator allows exploration of alpha distensibility using standardized methods. No significant change in alpha distensibility at follow-up suggests that alpha may be less modifiable in patients with long-standing pulmonary arterial hypertension.

**Key Words:** invasive cardiopulmonary exercise testing ■ pulmonary arterial hypertension ■ pulmonary hypertension ■ pulmonary vascular distensibility ■ right ventricular function

See Editorial by Raza and Chesler.

The right ventricle (RV) has considerable reserve in the face of increased afterload, but decreased RV function strongly associates with mortality in patients with pulmonary arterial hypertension (PAH).[1] RV function measurements including ejection fraction at rest must decrease >40% before there is a rapid progressive dilation in the RV, poor prognosis, and RV failure symptomatology. Invasive cardiopulmonary exercise testing (iCPET) is

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## CLINICAL PERSPECTIVE

### What Is New?

- The web-based interactive iCPET calculator tool standardizes the complex determination of alpha distensibility in individuals with multipoint pressure-flow measurements.
- The iCPET calculator is available at: https://vanderpoolrr.shinyapps.io/iCPET_calculator/.
- No significant changes in alpha distensibility at follow-up in patients with pulmonary arterial hypertension.

### What Are the Clinical Implications?

- The web-based iCPET calculator is a tool that can help facilitate the use of alpha distensibility in more clinical settings with standardized methods.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **CO** | cardiac output |
| **$E_a$** | arterial elastance |
| **$E_{es}$** | end-systolic elastance |
| **$E_{es}/E_a$** | right ventricular-pulmonary arterial coupling ratio |
| **ESP** | end-systolic pressure |
| **iCPET** | invasive cardiopulmonary exercise testing |
| **mPAP** | mean pulmonary artery pressure |
| **mPAP/Q** | slope of the multipoint pulmonary artery pressure-flow relationship |
| **PAH** | pulmonary arterial hypertension |
| **PAWP** | pulmonary artery wedge pressure |
| **PCA** | prostacyclin analogues |
| **PH** | pulmonary hypertension |
| **RHC** | right heart catheterization |
| **α** | alpha distensibility coefficient |

an important method for quantifying RV function under stressed conditions that is not possible with current resting measurements,[2–6] possibly enabling early detection of RV dysfunction in the disease course.[7] Exercise-induced changes in pulmonary arterial (PA) pressure, heart rate, cardiac output, RV contractility, and/or RV-PA coupling ratio are objective ways to assess the ability of the RV to adapt to altered afterload and stresses and RV contractile reserve.[7–11] Exercise hemodynamics can also be used to quantify distal vascular remodeling with the quantification of the pulmonary vascular distensibility.[12]

Using the Linehan distensible model of the pulmonary circulation, pulmonary vascular distensibility coefficient (α) can be determined from maneuvers that provide repeated measures of PA pressure, pulmonary artery wedge pressure (PAWP), and cardiac outpoint such as passive leg raises[13] or exercise hemodynamics.[12,14–16] Studies into pulmonary vascular distensibility (α) have focused on defining the upper limits of normal,[12,16] early detection of pulmonary vascular disease,[12,17,18] or the differential diagnosis of PAH from left-sided heart failure.[19] In a comprehensive paper, Malhotra et al[19] demonstrated decreased pulmonary vascular distensibility in patients with PAH (0.4%) compared with patients with normal pulmonary pressure (1%–2%) or heart failure (0.8%–0.9%). Pulmonary vascular distensibility is modifiable by vasodilatory therapy in patients with exercise pulmonary hypertension (PH)[18] and heart failure.[19] Pulmonary vascular distensibility has been found to associate with outcomes in patients with borderline PH and heart failure ejection fraction.[19,20] In a comprehensive study in patients with PAH, exercise PH, and heart failure preserved ejection fraction, pulmonary vascular distensibility was an independent predictor of peak RV-PA coupling.[7] RV diastolic stiffness, another measure of RV function, significantly associates with outcomes in patients with pulmonary hypertension[21] and is sensitive to 3 months of prostacyclin therapy in patients with PAH.[2]

While the clinical relevance of the pulmonary vascular distensibility coefficient has been demonstrated, the implementation requires clinical practitioners to use a complex set of markers in the analysis of exercise hemodynamics. An additional barrier to implementation is that the Linehan model of pulmonary vascular distensibility is a nonlinear equation (Equation 1) that requires custom programing in Excel, Matlab, RShiny or another data analysis program. Solving for the alpha distensibility coefficient α has led to varying implementations of the equation and analysis across centers.[16,18,22] Recent efforts have been made to standardize invasive cardiopulmonary exercise testing across centers in the PVDOMICS (Pulmonary Vascular Disease Phenomics) study.[23] The next step is to standardize the calculation of the pulmonary vascular distensibility coefficient and ultimately improve the quality and reproducibility of this analysis. Commercial and noncommercial software packages for the analysis of the distensibility coefficient are not available. In this paper, we introduce the iCPET calculator that is a multiplatform web-based exercise hemodynamics software tool. The calculator is designed to be user friendly with a graphical user interface that allows the user to input, modify, visualize, and save exercise hemodynamics using open-source tools. Considerations in the development of the calculator included the cost of the development platform (MATLAB, Python, and RShiny), accessibility of the tool to nonprogrammers, and the speed of the analysis.[24,25]

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Using this web-based analysis tool, we tested the hypothesis that decreased pulmonary vascular distensibility associates with reduced RV function and predicts therapeutic response in patients with pulmonary arterial hypertension. To do this, we investigated the therapeutic effect of PAH medication on pulmonary vascular distensibility in patients with PAH who had serial assessment of exercise hemodynamics. Specifically, we investigated associations between the change in pulmonary vascular distensibility with the change in (a) systolic RV function, and (b) diastolic RV function.

# METHODS

The program materials have been made publicly available at the Zenodo repository and can be accessed at https://zenodo.org/record/7789925. The clinical data that support the findings of this study are available from the corresponding author upon reasonable request.

## Study Population

Participants were identified from the UA PH (University of Arizona Pulmonary Hypertension) registry that had a right heart catheterization (RHC) and an invasive cardiopulmonary exercise test (iCPET, n=37 participants, RHC date of procedures between 2011 and 2018). Additionally, 32 participants had at least 2 iCPETs with at least 2 stages of exercise in addition to the resting RHC measurements (Figure 1A). Completeness of the RHC and iCPET data was evaluated and participants were excluded if they were missing key exercise data needed for the alpha distensibility calculations like exercise wedge pressure, cardiac output (CO), or mean PA pressure (mPAP; n=1 participant). This is a retrospective observational analysis with repeat visits. The earlier visit was labeled as the Index time point and the subsequent visit was labeled as the follow-up time point. The pulmonary hypertension diagnosis for the participants was verified by a physician based on the World Symposium of Pulmonary Hypertension guidelines.[26] Participants had a mix of pulmonary hypertension classifications and the current analysis focused on those with World Symposium of Pulmonary Hypertension group 1 PAH based on 2015 European Society of Cardiology/European Respiratory Society PH Guidelines[27] and a mixed group of participants with an mPAP <25 mm Hg (comparator group). One participant with World Symposium of Pulmonary Hypertension group 4 PH was excluded from the analysis (Figure 1A). A small control group (control, n=5) was also identified to validate the iCPET calculator. PAH-specific medications at the time of the index and follow-up RHC were recorded based on standard classes of medication including prostacyclin analogues (PCA), endothelin receptor antagonists, and phosphodiesterase 5 inhibitors and corresponding combinations of therapy including: oral combo therapy (phosphodiesterase 5 inhibitors+endothelin receptor antagonists), parenteral PCA+1 oral, parenteral PCA+2 oral, oral PCA+endothelin receptor antagonists/phosphodiesterase 5 inhibitors and parenteral PCA monotherapy. All participants gave informed consent through the Respiratory-Related Disease Patient (UA PH) Registry, which was approved by the institutional review board at the University of Arizona (Institutional Review Board Protocol no. 1100000621).

## Invasive Cardiopulmonary Exercise Testing

RHCs were performed in accordance with clinical guidelines. Briefly, a pulmonary artery catheter was inserted into the antecubital vein and advanced into the right atrium, RV, and into the pulmonary artery. Resting pressure including right atrial pressure, right ventricular pressure, mean pulmonary arterial pressure (mPAP) and PAWP. CO was measured by thermodilution and direct Fick method.

Following the resting RHC, participants underwent a symptom-limited incremental supine CPET with invasive pulmonary pressure and CO. Work rate was increased every 2 minutes following a step protocol with steps of 5, 10, 15, or 20 W depending on the patient's functional status. Peak exercise was determined either by a peak respiratory exchange ratio of >1.10 or symptom limitations. Breath-by-breath pulmonary gas exchange was recorded continuously to determine $O_2$ consumption during exercise. In the last minute of each exercise stage, mPAP and PAWP were recorded (Xper Cardio Physiomonitoring System; Phillips) and blood samples were drawn from the PA catheter to measure hemoglobin and $O_2$ saturation. CO was calculated by the direct Fick method ($CO=O_2$ consumption/arteriovenous $O_2$ difference). A radial arterial line was not used instead systemic $O_2$ saturation from pulse oximetry was used in the arteriovenous $O_2$ difference [arteriovenous $O_2$ difference=systemic–PA $O_2$ content]. Two pulse oximeters including a forehead probe were used on every patient without an arterial line.

## Pulmonary Vascular Distensibility and Compliance

Pulmonary vascular distensibility, a measure of distal vascular distensibility and pulmonary vascular compliance, a measure of global compliance, were both determined to quantify pulmonary vascular mechanics. Hemodynamics from the multistage invasive cardiopulmonary exercise testing were used to estimate the

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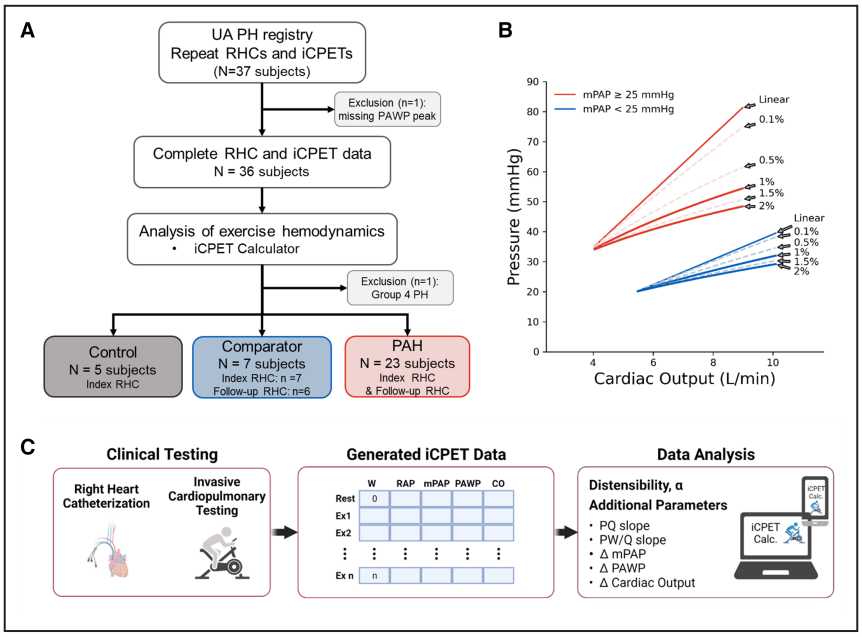


**Figure 1. Analysis of exercise hemodynamics and alpha distensibility in patients with and without pulmonary hypertension.**
**A**, Identification of participants from the University of Arizona Pulmonary Hypertension (UA PH) registry who had a right heart catheterization that included invasive cardiopulmonary exercise testing. The index visit included the control, comparator, and pulmonary arterial hypertension groups. The follow-up visit included only the comparator and pulmonary arterial hypertension groups. **B**, Theoretical pressure-flow relationships at different alpha distensibility in patients with a mean pulmonary arterial pressure of ≥25 mm Hg and <25 mm Hg. **C**, The generated invasive cardiopulmonary exercise testing hemodynamic data were analyzed for alpha distensibility as well as other metrics including the slope of the pressure-flow relationship for pulmonary arterial pressure (PQ slope) and wedge pressure (PW/Q slope) and the exercise-induced change in mean pulmonary arterial pressure, wedge pressure, and cardiac output. Created with BioRender.com. iCPET indicates invasive cardiopulmonary exercise testing; PAH, pulmonary arterial hypertension; PWAP, pulmonary artery wedge pressure; and RHC, right heart catheterization.

pulmonary vascular distensibility coefficient α using the Linehan distensibility model.

$$\mathrm{mPAP} = \left( \left[ (1+\alpha \times \mathrm{PAWP})^5 + \alpha \times \text{unstressed resistance} \times \mathrm{CO} \right]^{(1/5)} - 1 \right) / \alpha \quad (1)$$

where mPAP is a function of distensibility coefficient (α), pulmonary artery wedge pressure (PAWP), CO, and unstressed resistance.[15,16] Unstressed resistance is estimated by the ratio of mPAP and CO at rest (mPAP/CO). Theoretical pressure-flow relationships demonstrate the effect of alpha distensibility on the developed pressure at higher COs (Figure 1B).

PA compliance was calculated as the ratio of stroke volume to pulmonary artery pulse pressure [PA compliance=stroke volume/(systolic PAP–diastolic PAP)]. Stroke volume was determined as the ratio of CO and heart rate [stroke volume=CO/heart rate] and normalized by body surface area to determine stroke volume index. Pulmonary vascular resistance (PVR) was calculated as the ratio of [mPAP–PAWP] and CO. The pulmonary vascular resistance-compliance relationships were investigated and the RC-time constant was calculated as the product of PA compliance and PVR.

## RV Function

Single-beat analysis was used on RV pressure waveforms to assess RV function.[28–30] Max isovolumetric pressure was determined by fitting a sinusoidal curve to the early isovolumetric contraction and late isovolumetric relaxation regions of the RV pressure waveform. An algorithm was used to determine these regions defined by the first and second derivate of the pressure with respect to time.[28] Only minor manual modifications of these regions were allowed to optimize the sinusoidal fit. End-systolic pressure (ESP) was estimated from mPAP

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using the proposed equation ESP=1.65×mPAP—7.76 based on invasive conductance catheter measurements.[30] The end systolic elastance ($E_{es}$) was calculated as [max isovolumetric pressure–ESP]/stroke volume. Arterial elastance ($E_a$) was calculated as the ratio of ESP to stroke volume leaving the coupling ratio ($E_{es}/E_a$) as the ratio of [max isovolumetric pressure–ESP]/ESP. RV stroke work index was calculated as 0.0136×stroke volume index·[mPAP–right atrial pressure] in units of g/m/beat per $m^2$.

## iCPET Calculator Program Design

Invasive cardiopulmonary exercise tests generate a lot of data to be analyzed including workload, right atrial pressure, pulmonary artery pressure, wedge pressure and CO. Additional clinically meaningful parameters including the pressure-flow slopes and incremental change in pressure require additional calculations (Figure 1C). The development of the iCPET calculator by the team of engineers, pulmonologists, and physiologists focused on improving the analysis and interpretation workflow for iCPETs. Program design considerations included: (1) the need for a graphical user interface to enter, review and modify data; (2) the capability to generate the α distensibility coefficient and other hemodynamic parameters with 1 click; (3) the ability to save analysis and figures; (4) keeping the analysis local to protect patient data; (5) the ability to make the program platform agnostic and run without the requirement of expensive licenses or large support files; and (6) provides added value to current practices (Data S1; Figure S1). Modern data analysis programs have the tools and packages necessary to create such a program. The iCPET calculator was prototyped in 4 analysis solutions including Excel, Matlab, Python, and R/RShiny. The Matlab and RShiny versions of the iCPET calculator were used for repeated analysis of pulmonary hemodynamics in the identified patient cohort from the UA PH registry. Bland–Altman and intraclass correlation coefficient analyses were used to compare the calculation of distensibility, α, between the Matlab, and RShiny versions of the iCPET calculator to determine the effect of different implementations of the nonlinear fit to the measured data.

## Statistical Analysis

Results are expressed as mean±SD or median (interquartile range). A $P$ value <0.05 was considered significant. Comparisons between groups were made using a $t$ test or Mann–Whitney test, where appropriate. Repeated-measures analysis was performed to asses changes over time (index, follow-up) between the 2 groups (mPAP <25 and PAH). The lmer function in the lme4 package in R was used to construct repeated-measures linear mixed-effect models. Linear mixed models were used to determine the effects of PH type (PAH versus comparator), visit (index and follow-up) in Tables 1 and 2 for variables with only rest/single measurements at each time point. Variables with rest and peak exercise measurements, linear mixed models were used to determine the effects of PH type (PAH versus comparator), visit (index and follow-up), and exercise (rest and peak) with corresponding pairwise comparisons. The restricted maximum likelihood method was used in lmer and pairwise comparisons were made using the emmeans function. Results are shown in Tables 1 and 2. Correlations between alpha distensibility and PA compliance or age at the index and follow-up visit were calculated using Spearman correlation coefficients. The statistical analyses were performed using R programming language (r-project.org, version 4.1.1) and RStudio (version 1.4.1717).

# RESULTS

Twenty-eight participants were identified with complete RHC and iCPET data at an index and follow-up time point with a median follow-up time of 19 (8–28) months. Five participants with normal pulmonary pressure and no exercise PH with an index RHC were identified (control, age: 43±16 years, sex: 60% women). Participants with an index and follow-up RHC and an mPAP <25 mm Hg (mPAP <25) were classified as comparators. They had an average age of 67±5 years and a median follow-up time of 30.1 (16.2–42.6) months (Table 1). The comparator group includes a mix of no PH, exercise PH, and 1 participant with PAH but a resting mPAP <25 mm Hg. They were women (80%), non-Hispanic with an average body mass index of 34±16 $kg/m^2$. Participants with PAH had an average age of 54±13 years and a median follow-up time of 16.1 (5.8–23.8) months. They were predominately women (87%) and non-Hispanic (86%).

## iCPET Calculator to Analyze Exercise Hemodynamics

In this this project, we focused on the 4 very commonly available platforms of Excel, Matlab, Python, and R/RShiny for the development of an iCPET calculator. A more detailed discussion of the design considerations is included in Table S1 and details of the development in each platform are included in Figure S1. The current version of the iCPET calculator was designed to be usable on a desktop or laptop computer and on mobile devices using the R programming language and the RShiny Package (an R development tool for the development of the graphical user interface) (Figure 2). Additional information about the iCPET calculator is available on our GitHub repository (https://github.com/vanderpoolrr/iCPET_calculator). The user

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**Table 1. Demographics and Baseline Characteristics in Patients With Pulmonary Arterial Hypertension and a Comparator Group With Mean PA Pressure <25 mm Hg at Their Index and Follow-Up Right Heart Catheterization Visit**

| | Comparator (n=6) | | PAH (n=22) | |
|---|---|---|---|---|
| Visit | Index | Follow-up | Index | Follow-up |
| Women | 5 (83) | | 19 (87) | |
| Hispanic | 0 (0) | | 3 (14) | |
| Deaths | 0 (0) | | 2 (9) | |
| Age, y | 67±5 | | 54±13 | |
| PH type | | | | |
| No PH | 2 (33.3) | | | |
| Exercise PH | 3 (50) | | | |
| Idiopathic PAH | 1 (16.7) | | 11 (50) | |
| Drug- and toxin-induced PAH | | | 3 (13.6) | |
| Connective tissue disease | | | 2 (9.1) | |
| HIV infection | | | 1 (4.5) | |
| Portal hypertension | | | 2 (9.1) | |
| Congenital heart disease | | | 3 (13.6) | |
| Medication | | | | |
| No therapy | 3 (50) | 0 | 11 (50) | 0 |
| Oral combo therapy | 0 | 1 (16.7) | 1 (4.5) | 3 (13.6) |
| Parenteral PCA+1 oral | 2 (33.3) | 3 (50) | 4 (18.2) | 7 (31.8) |
| Parenteral PCA+2 oral | 1 (16.7) | 0 | 5 (22.7) | 8 (36.4) |
| Oral PCA+ERA/PDE5i | 0 | 1 (16.7) | 0 | 2 (9.1) |
| Parenteral PCA monotherapy | 0 | 1 (16.7) | 1 (4.5) | 2 (9.1) |
| Time between visits, mo | | 30.1 [16.2–42.6] | | 16.1 [5.77–23.8] |
| BMI, $m^2$ | 34±16 | 28±6 | 29±5 | 28±5 |
| RA pressure, mm Hg | 4±3 | 3.5±1 | 4±3 | 3.5±3 |
| RV ESP, mm Hg | 23±6 | 22±4* | 70±13*,† | 54±14*,†,‡ |
| $E_{es}$, mm Hg/mL | 0.60±0.43 | 0.62±0.25 | 1.41±0.76*,† | 1.15±0.58† |
| $E_a$, mm Hg/mL | 0.33±0.12 | 0.29±0.10 | 1.15±0.45*,† | 0.88±0.43*,† |
| $E_{es}/E_a$ | 1.89±1.22 | 2.54±1.51 | 1.25±0.55*,† | 1.46±0.82† |
| $E_{ed}$, mm Hg/mL | 0.25±0.18 | 0.26±0.15 | 0.80±0.51*,† | 0.55±0.21† |
| RVSWI, g/m/beat per $m^2$ | 8.0±2.4 | 8.8±2.4* | 20.6±5.8*,† | 16.1±5.1*,†,‡ |

Data presented as mean±SD, median [interquartile range], or number (percent). BMI indicates body mass index; $E_a$, arterial elastance; $E_{ed}$, end-diastolic elastance; $E_{es}$, end-systolic elastance; $E_{es}/E_a$, coupling ratio; ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PCA, prostacyclin analogue; PDEi, phosphodiesterase 5 inhibitor; RA, right atrium; RV ESP, right ventricular end-systolic pressure; and RVSWI, RV stroke work index.

*vs comparator index.

†vs comparator follow-up.

‡vs PAH index.

interface has a linear end-user experience that allows the user to start with the participant information and then enter the invasive hemodynamics into the RHC/iCPET stages table. After selection of the rest and exercise stages, the program analyzes alpha distensibility and determines the slope of the pulmonary artery, wedge and right atrial (RA) pressure-flow relationships. The RA pressure-flow relationship calculations are optional. Key components of the program are (1) the user's ability to verify and edit entered data in an interactive fashion and (2) the ability to save the analysis tables, figures and resulting analysis for later review and analysis (Figure S2). To assess the stability of the alpha distensibility calculations, the results from the Matlab and RShiny analysis programs were compared with determine interplatform variability (Figure 3A). There were no biases in the calculated alpha distensibility (bias: −0.002%/mm Hg, limits of agreement: −0.06% to 0.05%/mm Hg). The interobserver variability in the calculation of alpha distensibility using the RShiny app showed no biases in the calculated alpha distensibility (bias: −0.008%/mm Hg, limits of agreement: −0.115% to 0.099%/mm Hg; Figure 3B). Alpha distensibility values were compared between control (Table S2), comparators and PAH groups (Figure 3C). Alpha distensibility in the control group was 1.55% (1.53%–2.14%)/mm Hg and the comparator and PAH groups have a significant decrease in alpha

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**Table 2. Exercise Hemodynamics at Index and Follow-Up Invasive Cardiopulmonary Exercise Test**

| | Comparator (n=6) | | PAH (n=22) | |
|---|---|---|---|---|
| | Index | Follow-up | Index | Follow-up |
| Peak workload, Watt | 37 [35–51] | 32 [30–54] | 40 [30–44] | 45 [23–67] |
| Heart rate, bpm | | | | |
| Rest | 72±8 | 70±10 | 85±8*,† | 83±10*,† |
| Peak | 102±13* | 96±10† | 120±12‡,‖,# | 125±20§,‖,# |
| ΔHR | 30±13 | 26±6 | 34±13 | 42±20 |
| sPAP, mm Hg | | | | |
| Rest | 30±7 | 27±2* | 74±14*,† | 59±15*,†,‡ |
| Peak | 47±15* | 40±7†,‖ | 105±19‡,‖,# | 93±20§,‖,#,** |
| ΔsPAP | 17±9 | 12±5 | 31±15*,† | 33±14*,† |
| mPAP, mm Hg | | | | |
| Rest | 19±4 | 18±2 | 47±8† | 37±9*,†,‡ |
| Peak | 34±9* | 27±6†,‖ | 69±12‡,‖,# | 62±15§,‖,#,** |
| PAWP, mm Hg | | | | |
| Rest | 8±4 | 7±2 | 6±3 | 6±3 |
| Peak | 14±6* | 11±9† | 11±6‡ | 10±5§ |
| Cardiac index, L/min per $m^2$ | | | | |
| Rest | 2.8±0.7 | 3.1±0.6 | 3.0±0.6 | 2.9±0.7 |
| Peak | 5.2±1.6* | 5.2±1.1† | 4.8±1.4‡ | 5.5±2.1§ |
| ΔCI | 2.4±1.4 | 2.2±0.7 | 1.8±1.1 | 2.5±1.8 |
| Stroke volume index, mL | | | | |
| Rest | 39±6 | 45±13 | 36±8 | 36±10 |
| Peak | 50±11* | 55±14† | 41±13‡ | 43±11§ |
| ΔSVI | 11±8 | 10±7 | 5±9 | 7±13 |
| PVR | | | | |
| Rest | 2.1 [1.9–2.3] | 2.0 [1.5–2.3]* | 7.4 [5.6–9.3]*,† | 5.8 [4.3–7.0]*,†,‡ |
| Peak | 2.0 [1.3–3.0] | 1.7 [1.2–2.2]‖ | 6.6 [5.7–8.8]‖,# | 5.2 [4.6–6.3]‖,#,** |
| PA compliance | | | | |
| Rest | 4.8 [3.7–5.8] | 4.6 [4.5–5.7] | 1.5 [1.1–2.0]*,† | 2.0 [1.6 2.2]*,† |
| Peak | 4.8 [3.6–6.4] | 4.2 [3.9–4.9] | 1.2 [0.9–1.6]‖,# | 1.4 [1.2, 1.7]‖,# |
| Distensibility (α) | 0.7 [0.39–0.76] | 0.88 [0.70–0.98] | 0.13 [0.04–0.23]*,† | 0.17 [0.05, 0.26]*,† |
| Slopes | | | | |
| mPAP/Q | 3.0 [2.7–3.5] | 2.0 [1.5–3.1] | 6.0 [4.4–8.6]*,† | 5.4 [3.3–7.3]† |
| PAWP/Q | 1.4 [0.7–2.0] | 0.5 [−0.1–1.1] | 1.1 [0.4–1.8] | 1.2 [0.2–2.5] |

Data presented as mean±SD or median [interquartile range]. Rest condition: *vs index comparator—rest, †vs follow-up comparator—rest, ‡vs index PAH—rest, §vs follow-up PAH—rest. Exercise conditions: ‖vs index comparator exercise, #vs follow-up comparator exercise, **vs index PAH exercise. bpm indicates beats per minute; CI, cardiac index; HR, hazard ratio; mPAP, mean PA pressure; mPAP/Q, slope of the mean PA pressure to cardiac output relationship; PAWP, pulmonary artery wedge pressure; PAWP/Q, slope of the multipoint PAWP-flow relationship; PVR, pulmonary vascular resistance; Q, cardiac output; sPAP, systolic PA pressure; SVI, stroke volume index; and Δ, exercise—rest.

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distensibility that are in line with previously published results in larger cohorts.[7,19]

## Changes in Resting RV Function

Pulmonary vascular afterload decreased in participants with PAH between index and follow-up visits as measured by decreased mPAP (Figure 4A) and pulmonary vascular resistance (Figure 4B). There was a significant decrease in arterial elastance, a nonsignificant decrease in $E_{es}$ and resulting in no change in the coupling ratio Ees/Ea in the PAH group (Table 1). There were no significant changes in participants with an mPAP <25 mm Hg. RV stroke work index decreased in the participants with PAH, but there were no significant changes in RV diastolic stiffness at follow-up in both groups (Table 1).

## Exercise Hemodynamics

Similar workloads were achieved in patients with mPAP <25 mm Hg or PAH at their index or follow-up

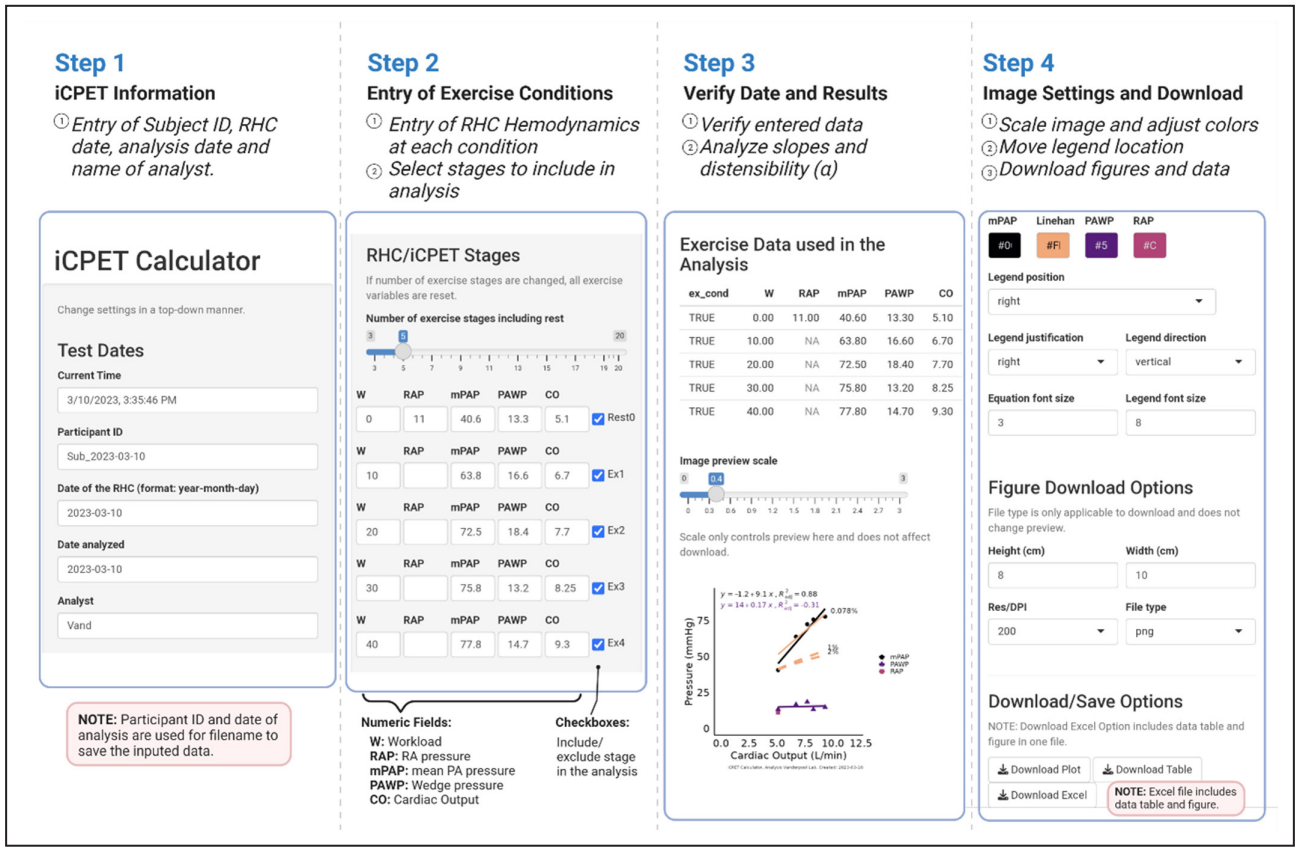


**Figure 2. Screenshots of the iCPET calculator on a mobile device.**
The iCPET calculator allows the user to enter the measured exercise hemodynamics and then calculate the slopes of the pressure-cardiac output relationships and alpha distensibility. The steps to use the app include: Step 1: The user enters information about the test including an identifying tag, date of the right heart catheterization/invasive cardiopulmonary exercise testing, date of the analysis, and the name of the analyst. Step 2: The number of exercise stages including rest are selected, and then the workload (W) and pressure data are entered into the resulting table. To increase flexibility, check boxes on the right-hand side are used to select exercise stages to be included in the calculations. Step 3: The entered data is displayed as a table and a figure to verify the entered results are correct. The figure allows the user to visually assess the pressure-flow relationships for mean pulmonary arterial pressure, wedge pressure, and right atrial pressure. Entering the right atrial pressure is optional. Step 4: The user can adjust settings for the figure including colors and legend location before selecting how to download and save the analysis. The downloaded Excel file will include the test information (patient ID, date of right heart catheterization, date analyzed, and analyst), exercise data from the entered table, alpha distensibility, and slopes of the pressure-flow relationships including the PQ slope and PW/Q slope. Created with BioRender.com. iCPET indicates invasive cardiopulmonary exercise testing; and RHC, right heart catheterization.

RHC (Table 2). In the patients with PAH at their index visit, they achieved a median workload of 40 (30–44) W with an exercise-induced increase in heart rate of 34±13 bpm, systolic PA pressure of 31±15 mm Hg, cardiac index of 1.8±1.1 L/min per $m^2$ resulting in a change of stroke volume index of 5±9 mL/$m^2$. There was no significant exercise-induced change in PVR or PA compliance. The slope of the mPAP-flow relationship (mPAP/Q slope) was 6.0 (4.4–8.6) mm Hg/L/min. At the follow-up visit, patients with PAH had similar exercise-induced increase in systolic PAP pressure, CO, and stroke volume. There was no significant change in the mPAP/Q slope at follow-up. In the participants with mPAP <25 mm Hg, the peak workload was 37 (35–51) W with an exercise-induced increase in hazard ratio of 30±13 bpm, systolic PAP pressure of 17±9 mm Hg, cardiac index of 2.4±1.4 L/min per $m^2$ and stroke index of 11±8 mL/$m^2$. At follow-up, there were no significant changes compared with the index visit. In comparison with participants with mPAP <25 mm Hg, participants with PAH had increased PVR, mPAP/Q slope and decreased PA compliance (Table 2). Participants with PAH had more of an exercise-induced increase in systolic PAP pressure compared with the mPAP <25 mm Hg group.

## PA Compliance and Alpha Distensibility

At the index RHC, exercise had minimal effect on the PA-compliance-PVR relationship (Figure 5A). There was a small shift down and to the left of the exercise resistance-compliance curve (Figure 5A, dashed line, [$Ca_{\_EX}$=9.12/(0.22+$PVR_{\_EX}$)]) compared with rest (Figure 5A, solid

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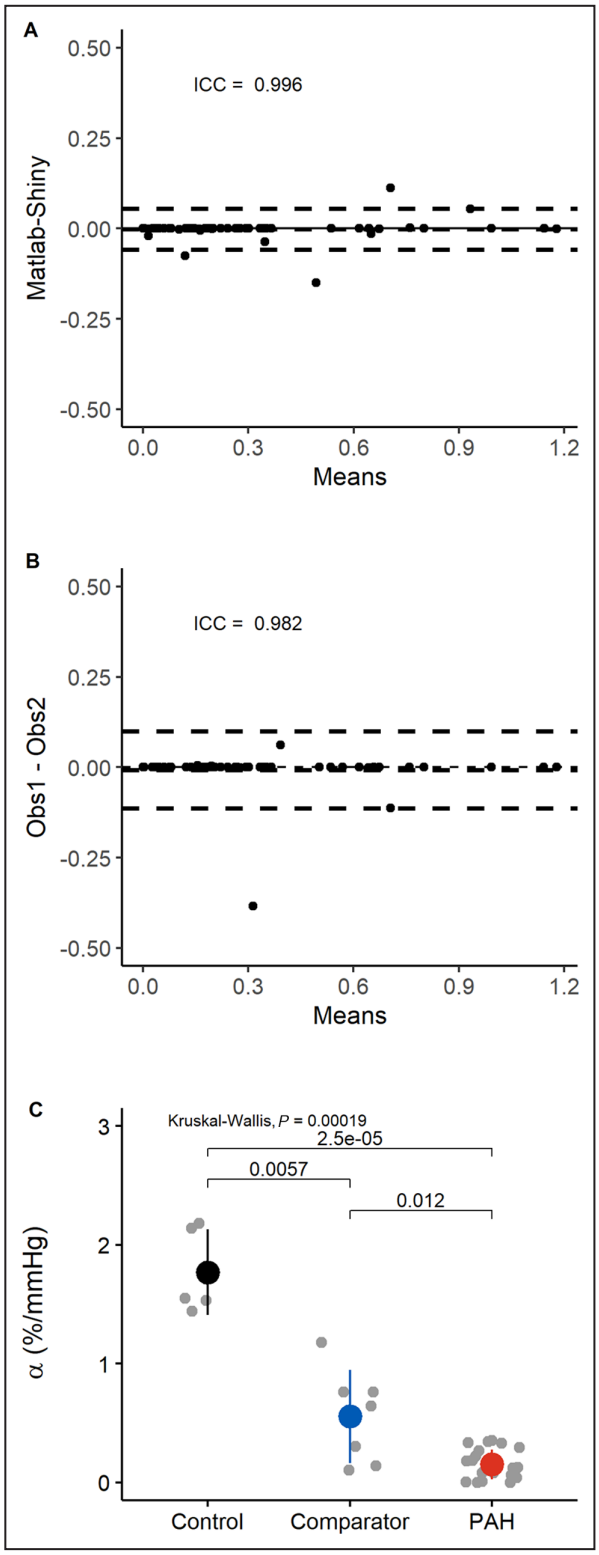


**Figure 3. Validation of iCPET calculator.**
Interplatform variability (**A**) and interreader variability (**B**) in the calculation of alpha distensibility. **C**, Comparison of alpha distensibility (α) between control, comparators, and pulmonary arterial hypertension groups. Data represented by mean±SD. ICC indicates intraclass correlation coefficient.

line, [$Ca_{-REST}$=12.16/(0.6+$PVR_{-REST}$)]) at the index time point. From Table 2, there were no significant exercise-induced changes in PA compliance or PVR at the index visit. At follow-up, PVR significantly decreased in participants with PAH (Table 2) but PA compliance did not significantly change due to the resistance-compliance relationship and the high index PVR. There were no significant changes in the rest resistance-compliance relationship (Figure 5B) and the exercise-induced changes in PA compliance or PVR. The resistance-compliance time (RC time) constant did not change between the index and follow-up visits in both groups (Figure 5C). At baseline, alpha distensibility was significantly decreased in the participants with PAH compared with participants with an mPAP <25 mm Hg (0.13% [0.04%–0.25%]/mm Hg versus 0.70% [0.39%–0.76%]/mm Hg, respectively, $P$<0.001). There was no significant change in alpha distensibility at follow-up in both groups (Figure 5D, Table 2). Alpha distensibility significantly correlated with PA compliance at the index (Figure 5E) and follow-up (Figure 5F) RHC.

## DISCUSSION

In this study, we developed a web-based analysis tool, iCPET Calculator, to analyze invasive cardiopulmonary exercise tests and standardize the application of the distensible vessel model [28] in patients with pulmonary hypertension. A retrospective cohort of participants was identified and follow-up changes in alpha distensibility were investigated. The tool was successfully deployed to calculate key hemodynamic parameters including distensibility with good agreement between the different users and implementations. No differences in alpha distensibility were noted between index and follow-up. Several factors could have contributed to this finding, including age of participants and the severity of PAH in the cohort.

### Standardizing Analysis of Alpha Distensibility With the iCPET Calculator

Calculation of alpha distensibility and the incremental slopes of the mPAP/Q and slope of the multipoint PAWP-flow relationship provide clinically meaningful information in the analysis and interpretation of invasive cardiopulmonary exercise testing. Four platforms (Microsoft Excel, Matlab, Python, and RShiny) were considered in the development of this analysis tool (Table S1). While most researchers have some level of experience with data analysis in Excel, distensibility calculations in Excel requires the use of the 'Solver' add-on and a degree of familiarity with optimization specific vocabulary. Determination of alpha in Excel also requires the user to have a relatively accurate guess for

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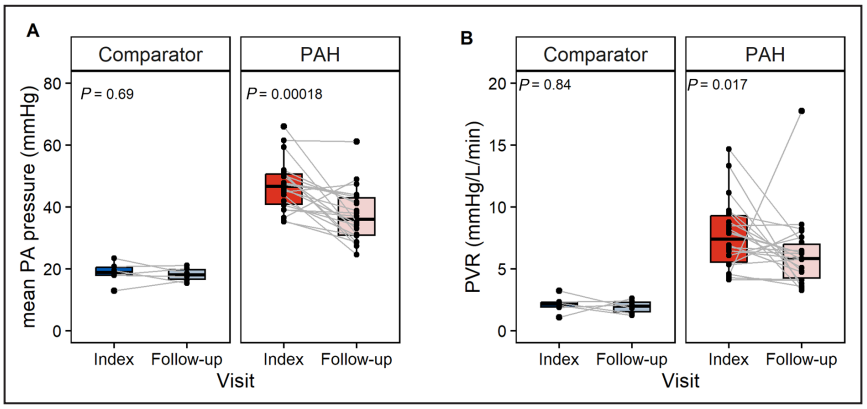


**Figure 4. Decreased afterload in patients with pulmonary arterial hypertension at follow-up.**

**A**, Patients with pulmonary arterial hypertension have decreased mean pulmonary arterial pressure at follow-up. There were no significant changes in patients with a mean pulmonary arterial pressure of <25 mm Hg (comparator). **B**, Decreased pulmonary vascular resistance in patients with pulmonary arterial hypertension. There were no significant changes in the comparator group. PA indicates pulmonary artery; PAH, pulmonary arterial hypertension; and PVR, pulmonary vascular resistance.

alpha distensibility to get an accurate result from the 'Solver' add-on. Reproducibility of the analysis steps are difficult in Excel because the user analysis steps are not saved for further review. The other 3 platforms (Matlab, Python, and RShiny) all have powerful optimization packages and the ability for the development of application specific graphical user interfaces that are specific to analyze exercise hemodynamics. These custom programs require minimal user input. Analysis tools developed in Matlab and Python still required the user to download and install additional programs and environments. The web browser-based application for the iCPET calculator in R as an RShiny application allows users to use the calculator without needing to install additional software. RShiny applications have been beneficial in the analysis of RNAseq data with the development of a browser-based application for differential expression analysis.[24] The flexibility of RShiny framework as a web-based program provides cross-platform compatibilities along with the excellent data visualization. It is possible to add in additional features and analysis in the future as new clinically important exercise hemodynamic variables are identified. Another consideration in the alpha distensibility calculations is the number of exercise stages necessary in the calculations. Alpha distensibility is sensitive to local variability in pressure-flow measurements (Figure S3). However, Kozitza et al found no significant differences in alpha distensibility when they just used passive leg raise peak exercise.[13] These findings suggest that increase in blood flow from the passive leg raise is enough to elicit a similar response of the small arterial pulmonary circulation as an exercise-induced increase in CO/volume. Alpha distensibility from a passive leg raise showed significant differences between control, isolated postcapillary PH, combined pre- post-capillary PH and PAH that were identical the peak exercise-based calculations. The interactive ability to include/exclude specific exercise/measurement stages allows the user to explore the impact of specific measurements (eg, number of exercise stages) on alpha distensibility. The iCPET calculator provides a workflow that helps to reduce user errors and standardizes alpha distensibility calculations.

## Changes Over Time in mPAP/Flow Slopes

Increased age and severity of pulmonary vascular remodeling have both been found to significantly impact the mPAP/CO (mPAP/Q) slope. Definitions of exercise pulmonary hypertension were re-introduced in the 2022 European Society of Cardiology/European Respiratory Society PH guidelines as an mPAP/Q slope of >3 mm Hg/L/min.[31] Individuals with elevated mPAP/Q slopes have increased risk for future cardiovascular or death events.[32] Age is another factor that impacts the upper limit of normal for the mPAP/Q where the upper limit of normal decreases to 2.73 mm Hg/L/min in individuals aged >50 years.[33] In our study, the participants with an mPAP <25 mm Hg do not have a "normal" pulmonary vasculature with an mPAP/Q slope of 3.0 (interquartile range, 2.7–3.5) mm Hg/L per minute. At follow-up, there was no significant change in the mPAP/Q slope (2.0 mm Hg/L/min) where the older age of the participants in this group (67±5 years) may have contributed to these results. For the participants with PAH, they had elevated mPAP/Q slopes (6.0 [4.4–8.6] mm Hg/L per min) that are consistent with significant pulmonary vascular remodeling. At follow-up in the PAH group, there was not a significant change in mPAP/Q slopes.

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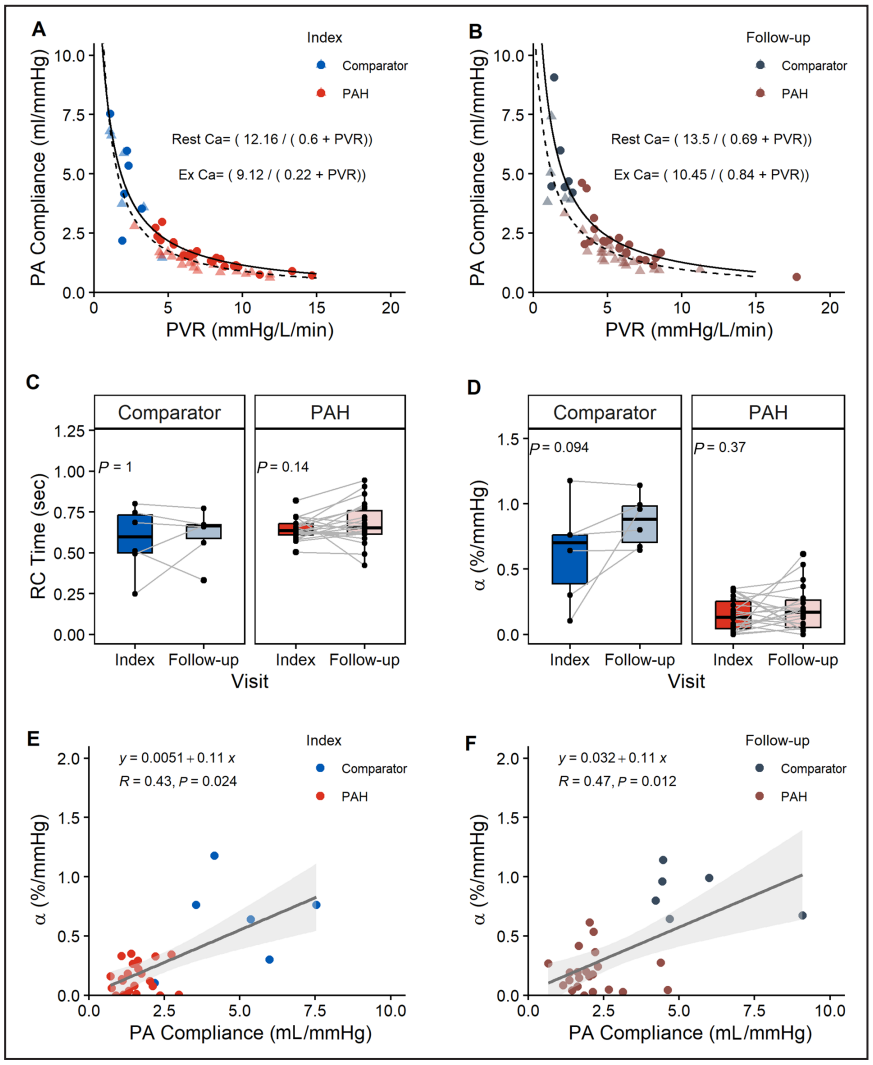


**Figure 5. Alpha distensibility in context to the resistance-compliance relationship, pulmonary arterial compliance, and resistance-compliance time (RC-time).**
**A**, Inverse relationship between pulmonary arterial compliance and pulmonary vascular resistance in patients with pulmonary arterial hypertension and comparator group at rest (circle) and peak exercise (triangle) at the index time point. The exercise resistance-compliance curve (dashed line) had a small shift down and to the left compared with rest (solid line). **B**, Resistance-compliance relationship at the follow-up time point. The exercise resistance-compliance curve (dashed line) had a shift down and to the left compared with rest (solid line). **C**, No significant differences in RC-time between index and follow-up right heart catheterization in both comparator and pulmonary arterial hypertension groups. **D**, No significant change in alpha distensibility (α) between index and follow-up visit for patients with pulmonary arterial hypertension and without pulmonary hypertension. Pulmonary arterial compliance significantly correlates with alpha distensibility at the index (**E**) and follow-up (**F**) time points. PA indicates pulmonary artery; PAH, pulmonary arterial hypertension; and PVR, pulmonary vascular resistance.

## Changes Over Time in Pulmonary Vascular Stiffness and Distensibility

Recent papers have demonstrated the functional relevance of alpha distensibility in patients with mild or exercise PH. In a normal range of alpha distensibility (1%–2%), the vasculature is able to expand to accommodate the increase in CO with minimal increase in pressure (Figure 1B). Alpha distensibility has been shown to decrease with exercise PH, heart failure preserved ejection fraction and PAH resulting in a more dramatic effect on exercise induced increases in pressure.[7,19] In a subset of patients with RV pressure tracings with exercise, alpha distensibility significantly

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associates with exercise RV-PA coupling.[7] Alpha distensibility has been found to be modifiable in patients with heart failure reduced ejection fraction[19] and exercise PH.[18] When compared with placebo, 12 weeks of sildenafil treatment significantly increased alpha distensibility by 24.6% in patients with heart failure reduced ejection fraction.[19] In another mixed population of patients diagnosed with exercise PH, Wallace et al measured an increase in alpha distensibility from 0.69±0.15%/mm Hg to 1.15±0.27%/mm Hg after 9.4±4 months of vasodilator therapy.[18] The partial reversal of vascular distensibility with vasodilatory therapy suggests that alpha distensibility can be used as a marker of vascular beds response to therapy. In our study, patients with PAH did not have a significant change in alpha distensibility at their follow-up iCPET despite significant decrease in pulmonary vascular resistance and afterload (Figure 5D). At follow-up, all PAH participants who were on PH medications did have decreased pulmonary vascular resistance, but some patients had a decrease in alpha (index: 0.26 [0.14–0.33], follow-up: 0.08 [0.03–0.19], *P*=0.018). One potential explanation is the differential therapy of these patients but the admixture of therapy was similar between those with increased and decreased alpha (Figure S4). Alternatively, these patients may have had more severe degree of pulmonary vascular remodeling with the lower starting alpha distensibility of 0.13% [0.04%–0.25%]/mm Hg and decreased global PA compliance compared with the group with improvement in alpha.

Alpha distensibility might be less modifiable in patients with advanced PAH and elevated PVR and therefore less effective at measuring therapeutic changes due to fairly advanced stages of pulmonary vascular remodeling. Alpha distensibility might act in a similar fashion as PA compliance in the resistance compliance curve (Figure 5A and 5B)[34] where compliance is less modifiable when PVR is high. In patients with exercise PH or mild-normal range of alpha distensibility, Langleben et al recently demonstrated there is still the ability for pulmonary capillary recruitment in addition for vascular distention during exercise.[35] The increase in alpha distensibility that Wallace et al found in their cohort of exercise PH cohort could potentially be explained by increased pulmonary capillary recruitment following pulmonary vascular therapy. In their cohort, resting mPAP decreased from 24.1±1.7 mm Hg pretreatment to 21.6±1.3 mm Hg post-treatment. While they found no change in resting PA compliance with treatment, they did show an increase in PA compliance at peak exercise.[18] We might speculate that in pulmonary capillary recruitment is significantly reduced in patients with advanced pulmonary vascular remodeling that is less modifiable by pulmonary vasodilator therapy. In our cohort of patients with advanced PAH, resting PVR decreased at follow-up (Table 2) but there were no significant changes in rest and exercise PA compliance and alpha distensibility. Based on the resistance-compliance relationship, there likely needs to be a large decrease in PA pressure and PVR for there to be a significant increase in alpha distensibility that is more difficult to achieve in patients with severe PAH with high PVR. When alpha distensibility is plotted as a function of PVR, there is an inverse relationship (Figure S5). Further suggesting that it takes a significant decrease in PVR to see an increase in alpha distensibility and that it might be more modifiable in early disease states before significant increases in PVR and long-standing disease.

The Linehan distension model measures the distension of the resistive vessels and a key assumption in the model is that the resistive segments are fully recruited including the arteriolar, capillary and venular portions. Additional studies are needed to investigate the loss of capillary recruitment in advanced forms of PAH and whether it is modifiable with pulmonary vasodilatory therapy. Pulmonary vascular therapies that dilate the pulmonary vasculature but not reverse pulmonary vascular remodeling may not lead to significantly improved exercise induced changes in the vasculature (eg, recruitment). Thus, with vasodilatoy therapy, vessels are more dilated at rest reducing resting resistance but if there is no change in vascular stiffness there will still be a significant exercise-induced increase in pressure based on alpha distensibility and the mPAP/Q slope. Alpha distensibility might be more modifiable in patients with advanced PAH with new PAH therapies like Sotatercept that more directly target pulmonary vascular remodeling through the bone morphogenetic protein signaling pathway.[36]

## Limitations

There are several limitations to the present study. The participants with an mPAP <25 mm Hg are not representative of a control population. Their alpha distensibility was 0.7% [0.39%–0.76%]/mm Hg suggest a degree of pulmonary vascular remodeling compared with a control population.[7] In fact, a few subjects had pressures between 20 and 25 mm Hg and could be classified as having pulmonary hypertension under the new World Symposium of Pulmonary Hypertension guidelines.[37] The cohort was retrospectively derived from the UA PH registry resulting in a cross-sectional view of participants with PAH at various stages of disease progression and therapeutic treatments. The use of pulse oximetry instead of an arterial line to measure systemic $O_2$ saturation in the Fick CO calculations could be a source of error, especially in patients with scleroderma or other conditions that

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reduce the accuracy pulse oximetry. Two pulse oximeters were used on every patient without an arterial line. In our experience, we placed one of the probes on the forehead as we find it to be more reliable in the context of Raynaud's and connective tissue disease. Age is another factor to consider with interpreting the exercise response and alpha distensibility. Oliveira et al. demonstrated that subjects <50 and ≥50 years old have different responses to exercise that result in different upper limits of normal.[33] In the present study, only 8 participants were <50 years old and their PQ slope ranged from 1.4 to 21.6 at the index RHC. There was no significant correlation between age and alpha distensibility at the index RHC but there was 1 at the follow-up RHC (Figure S6). Length of follow-up is another factor that could have had an influence with variable follow-up times from 3 months to 4.7 years. The change in alpha distensibility was not a function of the follow-up times, but therapeutic strategies could have had a contributing factor in this retrospectively identified cohort.

## CONCLUSIONS

In this retrospective cohort analysis, we found limited changes in alpha distensibility with treatment in patients with PAH despite a decrease in pulmonary vascular afterload (PVR and mPAP) at follow-up. The RShiny iCPET calculator standardizes and improves the reproducibility of the alpha distensibility calculations. Additional prospective studies are needed to investigate alpha distensibility as a clinical meaningful marker to study therapeutic effects in patients with advanced PAH and elevated PVR.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Material

Data S1
Tables S1–S2
Figures S1–S6

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