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Pulmonary Hypertension and Exercise

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Key Points

- Pulmonary hypertension (PH) has severe cardiopulmonary consequences that usually manifest with exertional dyspnea and exercise intolerance.
- Cardiopulmonary exercise testing (CPET) helps magnify the aberrant physiology of PH, which has both diagnostic and prognostic utility in PH.
- Physiologic abnormalities in PH can include reduced cardiac output, aerobic capacity, anaerobic threshold, inefficient ventilation, dynamic hyperinflation, peripheral muscle dysfunction, and dyspnea.
- Important CPET variables in PH include: $\text{VO}_{2\text{peak}}$, WR_{peak} , O_2 pulse, $\text{V}_\text{D}/\text{V}_\text{T}$, $\text{V}_\text{E}/\text{VCO}_2$, P_{etCO_2} , PaCO_2 , peak systolic pressure, and exercise duration.
- Clinical trials have used variables from CPET as primary efficacy outcomes, yet few trials evaluate the efficacy of exercise training as adjuvant therapy in PH
- Exercise training with light-intensity endurance, strength, and respiratory training is safe and beneficial in PH, and merits further consideration.

Synopsis (100 words)

Cardiopulmonary exercise testing can be a useful tool for clinicians working pulmonary hypertension (PH) patients. Exercise magnifies numerous cardiopulmonary decompensations, which can help inform diagnoses, assess degrees of physical impairment, evaluate exertional dyspnea and estimate prognoses for PH patients. Supervised exercise training also holds promise in PH, as it is safe for patients, feasible, and may improve key prognostic outcomes that relate to improvements in quality of life and survival. Still, few clinical trials have evaluated the potential therapeutic effects of exercise training, and future trials may benefit from integrating programming that focuses on light-intensity endurance, strength, and respiratory training.

Abbreviations

6MWD – distance covered during 6-minute walk test

AT – anaerobic threshold

CPET – cardiopulmonary exercise testing

CTEPH – chronic thromboembolic pulmonary hypertension

HR – heart rate

mPAP – mean pulmonary artery pressure

PaCO₂ – partial pressure of arterial CO₂

PAH – pulmonary arterial hypertension

PH – pulmonary hypertension

PCO₂ – partial pressure of CO₂

P_{et}CO₂ – end-tidal partial pressure of CO₂

\dot{V} CO₂ – CO₂ output

V_D/V_T – ratio of physiologic dead space over tidal volume

\dot{V}_E – minute ventilation

$\dot{V}O_2$ – O₂ consumption

$\dot{V}O_{2peak}$ – peak O₂ consumption

WR – work rate

Introduction

Pulmonary hypertension (PH) is a condition wherein the resting mean pulmonary artery pressure (mPAP) is pathologically elevated $\geq 25\text{mmHg}$.¹ Several physiological processes can produce PH, and these are reflected in the five different classes of PH (see Table 1).² For example, pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH) represent two distinct classes of PH affecting pre-capillary sites within the pulmonary vasculature. In addition to idiopathic causes, PAH can result from genetic mutations, drugs and toxins, connective tissue disorders, infections (e.g., HIV and schistosomiasis), portal hypertension, and congenital heart abnormalities. In contrast, CTEPH is a consequence of a pro-inflammatory remodelling in response to pulmonary thromboembolism, which causes persistent structural changes that obstruct pulmonary vasculature. Altogether, PH is rare but its prevalence continues to increase.³ A diagnosis of PH, irrespective of the underlying cause (i.e., groups 1-4 inclusively) presents an especially unfavorable prognosis of a seven-fold increase in 1-year mortality.³

Exercise intolerance is an ominous early warning sign common in, but not specific for PH.¹ The added demand placed on the cardiopulmonary system during exercise magnifies the aberrant pathophysiology in PH,⁴ and accordingly, PH patients report significantly greater levels of physical inactivity, dyspnea and sedentary time.⁵⁻⁷ Together, the pairing of physiological and behavioral limitations produce a debilitating spiral of deconditioning that ultimately leads to even greater levels of fatigue,⁸ and much poorer quality of life.^{9,10} Herein, we discuss the cardiorespiratory manifestations of PH, review the potential diagnostic and prognostic utility of cardiopulmonary exercise testing (CPET), and look towards the potential role of exercise training as adjuvant therapy for PH.

Exercise Pathophysiology in Pulmonary Hypertension

General hallmarks

The physiological derangements of PH result in characteristic abnormalities observed during dynamic exercise and often lead to dyspnea and exercise intolerance, which are summarized in Figure 1 and will be discussed in the following chapters. Impaired cardiac function results in reduced aerobic capacity, anaerobic threshold (AT), and oxygen consumption ($\dot{V}O_2$).¹¹⁻¹⁶ Both high physiologic dead space (i.e., as measured by the ratio of physiologic dead space [V_D] over tidal volume [V_T]: V_D/V_T) and chemosensitivity contribute to an elevated ratio of minute ventilation (\dot{V}_E) to CO_2 output ($\dot{V}CO_2$; expressed as $\dot{V}_E/\dot{V}CO_2$) during CPET.¹⁷⁻²⁵ Consequently, resting hypocapnia with low end-tidal PCO_2 ($P_{et}CO_2$) throughout exercise are typically observed and are related to the severity of disease.^{18,26-29} Exertional hypoxemia is also a common finding during exercise, which can be related to ventilation-perfusion heterogeneity, low mixed venous O_2 content from impaired cardiac output, and right-to-left shunting through a patent foramen ovale.³⁰ Even in the absence of significant resting airflow obstruction, dynamic hyperinflation can occur in pulmonary vascular diseases, which contributes to exertional dyspnea and exercise intolerance.³¹⁻³³ Peripheral muscle dysfunction is another common component of exercise pathophysiology in these conditions.³⁴⁻³⁷

Low cardiac output, ventilatory inefficiency, abnormal lung mechanics, hypoxemia and skeletal (peripheral and respiratory) muscle dysfunction contribute, to variable degrees, to decreased exercise tolerance in patients with PH.

Cardiovascular anomalies

Elevated mPAP from increased pulmonary vascular resistance has profound deleterious effects on the cardiovascular system. Early in PH, the distensibility of the pulmonary vasculature

is compromised,³⁸ impairing right ventricular outflow and thus increasing its afterload.³⁹ As such, left atrial filling (i.e., preload) is limited by a reduction in blood flow through the lungs from the right heart,^{12,40-42} and even further restricted by a leftward shift in the interventricular septum due to the overloaded right ventricle.^{11,12} Ultimately, this decompensated cardiac morphology limits cardiac output and stroke volume, which has functional and prognostic implications.^{13,14}

Stroke volume impairments become problematic during exercising conditions, as increased metabolic demands of active peripheral muscles require proportional increases in cardiac output, which then must inefficiently hinge on changes in heart rate (HR) to a much greater degree.⁴³ A blunted cardiac output response during exercise that relies heavily on changes in HR has a number of consequences, including a reduced aerobic capacity ($\dot{V}O_{2\text{peak}}$), and flattened oxygen pulse ($\dot{V}O_2/\text{HR}$) during CPET.^{15,16} Conformational abnormalities in the microcirculation of skeletal muscles and lower type 1 muscle fibre density in PH further impairs peripheral oxygen use and limits overall muscle strength.³⁴⁻³⁷ As such, peak work rates (WR) are reduced in PH but usually the ratio of $\dot{V}O_2/\text{WR}$ also remains low (see Figure 2),⁴⁴ indicative of impaired cardiovascular function and/or abnormal oxygen utilization peripherally.^{15,16,18} Therefore, PH patients rely on anaerobic metabolism to a greater degree and at lower levels of work than healthy individuals, reflected in a reduced AT.¹⁵ Collectively, these abnormal responses to exercise help explain the cardiovascular determinants of why PH patients report disproportionately elevated levels of work-related dyspnea (see Figure 3a).¹⁹

Impaired cardiac function in PH is reflected in reduced $\dot{V}O_{2\text{peak}}$, WR, $\dot{V}O_2/\text{WR}$, and AT. Abnormal skeletal musculature is superimposed on impaired cardiac function, resulting in disproportionately higher levels of ventilation and work-related dyspnea.

Ventilatory anomalies

A mismatch between low capillary perfusion and well ventilated alveoli is characteristically found in PH, thus the volume of ventilated lung not involved in gas exchange (i.e., physiological dead space; V_D/V_T) is increased.¹⁷⁻²⁰ To compensate for this ventilation-perfusion mismatch, patients must increase their minute ventilation (\dot{V}_E), which contributes to inefficient ventilation for a given $\dot{V}CO_2$ (high $\dot{V}_E/\dot{V}CO_2$).^{15,21,45} Unfortunately, respiratory muscle weakness is also common in PH and results in reduced maximal inspiratory and expiratory strength.^{32,46,47} Therefore, patients often rely on rapid and shallow breathing during exercise. A rapid shallow breathing pattern may also be observed as a consequence of sympathetic hyperstimulation from chemoreflexes and metabo-reflexes.²¹ Still, some PH patients demonstrate dynamic reductions in inspiratory capacity (see Figure 4)¹⁹ in the absence of respiratory muscle fatigue, suggestive of true dynamic hyperinflation, likely a consequence of mild expiratory airflow limitation that may be undetectable at rest but becomes pronounced during rapid breathing.³¹⁻³³ This dynamic hyperinflation likely further intensifies perceptions of excessive dyspnea during exercise,³³ beyond what would be expected at given \dot{V}_E (see Figure 3b).¹⁹

A consequence of increased \dot{V}_E is a low $P_{et}CO_2$, but during incremental exercise, the body metabolically produces more carbon dioxide (higher $\dot{V}CO_2$), so normally $P_{et}CO_2$ increases. In PAH however (see Figures 5a and 5b),⁴⁴ patients increase their \dot{V}_E disproportionately to the rise in $\dot{V}CO_2$,^{16,27,28,48-51} resulting in decreasing $P_{et}CO_2$.^{18,26-29} Similarly, this abnormality can be seen when comparing the arterial partial pressure of carbon dioxide ($PaCO_2$) to $P_{et}CO_2$ ($P_{(a-et)}CO_2$), whereby $P_{et}CO_2$ in patients with pulmonary vascular disease are lower than the $PaCO_2$ (resulting

in positive $P_{(a-et)}CO_2$ difference) versus the inverse (a negative $P_{(a-et)}CO_2$ difference) in healthy individuals.^{19,29,52} Although patients are hypocapnic at rest and during exercise, the $P_{(a-et)}CO_2$ is positive at peak because of the characteristic rapid shallow breathing pattern (low V_T , high breathing rate) that results from sympathetic over-stimulation, so there is less expiratory time for the $P_{et}CO_2$ to rise relative to the reduction in $PaCO_2$ from alveolar hyperventilation.²¹ Though this exercise hyperventilation and hypocapnia is likely in part due to a compensation for the increased V_D/V_T , PH patients may also possess altered lower arterial CO_2 setpoints and exaggerated chemoreflexes which inappropriately increases V_E despite already low CO_2 levels.²¹⁻

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Increased exertional ventilation on exercise (high V_E/VCO_2) is a key abnormality in PH reflecting increased wasted ventilation, enhanced chemoreflexes, and a decrease in the arterial CO_2 set point, the latter two being consequences of increase afferent sympathetic stimuli.

Diagnostic Utility of Cardiopulmonary Exercise Testing

While right heart catheterization serves as the gold-standard diagnostic test for PH,¹ CPET unveils the magnification of the aberrant physiology during exercise to provide additional non-invasive metrics that can be used diagnostically or for prognostication (see Figure 6).⁴⁴ For example, CPET can be useful in distinguishing PH patients from those with other cardiopulmonary abnormalities, or even between the different types of PH. While several abnormal parameters are shared between PAH and chronic left heart failure patients, their magnitude of dysfunction can help separate the two patient groups. For example, higher $\dot{V}_E/\dot{V}CO_2$ slopes and V_D/V_T , as well as lower $P_{et}CO_2$ and O_2 pulse are found in PAH versus those in left heart failure.^{16,53} Furthermore, PAH patients also frequently experience exertional hypoxemia while stable left heart failure patients do not.^{16,53} Despite similar presentations of high $\dot{V}_E/\dot{V}CO_2$

and chemosensitivity in both PAH and left heart failure patients, a pattern of oscillatory breathing during exercise may be observed in left heart disease that does not occur in PAH.⁴⁹

CPET can also be useful in distinguishing between precapillary PH subgroups. Specifically, CTEPH patients have more pronounced vascular obstruction than PAH, and thus higher dead space. This leads to greater ventilatory demand (\dot{V}_E peak and at the AT), and more inefficient ventilation (\dot{V}_E - $\dot{V}CO_2$ slope and $\dot{V}_E/\dot{V}CO_2$ ratio at the AT) on CPET.²⁷ Moreover, a $P_{(a-et)}CO_2$ greater than 7mmHg discriminated patients with CTEPH from PAH with a sensitivity of 88% and specificity of 90%.²⁹ Similarly, a composite score factoring \dot{V}_E - $\dot{V}CO_2$ slope, $P_{et}CO_2$ at the AT, alveolar-arterial oxygen pressure gradient at peak exercise, and $P_{(a-et)}CO_2$, identified CTEPH with a sensitivity of 83% and specificity of 92%, despite patients having normal or undetectable right ventricular dysfunction on echocardiogram.⁵⁴

Cardiopulmonary Exercise Testing for Prognostic Evaluation

Results from CPET can also be useful indicators of disease severity and prognosis. For example, low peak systolic blood pressures (≤ 120 mmHg) during exercise and reduced peak aerobic capacity ($\dot{V}O_{2peak} \leq 10.4$ ml/kg/min) are indicators of poorer survival in PH.⁵⁵ While similar studies have echoed the relationship between poor aerobic capacity and survival,⁵⁶ others have added that inefficient ventilation (e.g., elevated \dot{V}_E - $\dot{V}CO_2$ slope and $\dot{V}_E/\dot{V}CO_2$ ratio at the AT), and delayed post-exercise heart rate recovery also portend a higher risk of mortality.^{18,57-59} Interestingly, CPET may be particularly useful in identifying exercise-induced right-to-left shunt through a patent foramen ovale. These conditions of significantly elevated right atrial pressures leading to patency of a shunt can be seen when $P_{et}CO_2$ and O_2 saturations drop precipitously during exercise; a finding that carries a 65% increased risk of 5-year mortality.³⁰

CPET is a valuable tool for prognostic assessment in PH. Low peak systolic blood pressure, low $\dot{V}O_{2\text{peak}}$, a very high $\dot{V}_E/\dot{V}CO_2$, and identification of exercise-induced shunt are common worrisome findings that relate to reduced patient survival.

Exercise Variables as Clinical Trial Efficacy Endpoints

Because of their link with important clinical outcomes, exercise variables serve as common efficacy endpoints for clinical trials. In PAH for example, intravenous prostacyclin dramatically improves $\dot{V}O_{2\text{peak}}$,⁶⁰ and sildenafil showed promise in improving $\dot{V}O_{2\text{peak}}$, O_2 pulse, $\dot{V}_E/\dot{V}CO_2$, and $P_{\text{et}}CO_2$.⁶¹ In CTEPH, pulmonary endarterectomy serves as the preferred definitive treatment option because it improves survival and coincidingly, numerous CPET variables as well (e.g., $\dot{V}O_{2\text{peak}}$, $\dot{V}_E-\dot{V}CO_2$ slope, $\dot{V}_E/\dot{V}CO_2$ ratio at the AT, V_D/V_T , and $PaCO_2$).⁶² CPET has also shown that inoperable CTEPH patients may benefit from balloon pulmonary angioplasty (e.g., improved $\dot{V}O_{2\text{peak}}$, WR_{peak} , O_2 pulse, V_D/V_T , $\dot{V}_E-\dot{V}CO_2$ slope, and exercise duration) or pharmacotherapy with phosphodiesterase-5 inhibitors or endothelin receptor antagonists (e.g., improved $\dot{V}O_{2\text{peak}}$, WR_{peak} , O_2 pulse, and V_D/V_T).^{63,64} Despite guidelines now recommending supervised exercise training for deconditioned patients receiving medical therapies,¹ few trials have examined the potential synergistic effects of pharmacotherapy plus structured exercise training,⁶⁵ perhaps due to safety concerns or lacking specific recommendations detailing targeted exercise programming.

Exercise training in pulmonary hypertension

Safety considerations for programming

Prior to the availability of effective therapies for PAH, it was recommended that strenuous physical activity be avoided due to a perceived risk of syncope, sudden death, and worsening right heart failure.^{65,66} However, the safety of exercise training in PH has now been

well established. A meta-analysis of 16 trials including 469 patients found an overall risk of adverse events during exercise training at 4.7% and syncope being a rare occurrence (< 1 %).⁶⁵ Furthermore, no deaths and no episodes of worsening right heart failure occurred during these studies. The potential risks of exercise can be mitigated by taking appropriate precautions.⁶⁷ For example, the risk of exertional pre-syncope and syncope can be minimized by ensuring patients with PH are stable and on optimal medical therapies. Weight training which focuses on single muscle groups (rather than complex movements using multiple muscle groups) using low weights and high repetitions dampens the effect of Valsalva maneuvers on right heart filling and function. The risk of syncope, arrhythmia and palpitations can be minimized by avoidance of high intensity exercise, maintaining effort at less than 80% of the maximal work load or heart rate. During initial exercise training sessions, supervision and frequent monitoring of vital signs are essential to detect hypotension and oxygen desaturation.

Exercise training in PH can be safe when patients are stable on optimal medical therapies, avoid high-intensity training regimens, and are supervised while they acclimate to the program during their initial sessions.

Preliminary efficacy of exercise trials

Exercise training programs have the potential to improve muscle strength, endurance, peak exercise capacity, quality of life, and pulmonary hemodynamics in PH patients. In a study of 19 stable idiopathic PAH patients, a 12-week program of cycle endurance and quadriceps strength training led to 34% and 13% improvements in endurance time and quadriceps strength, respectively.⁶⁸ These improvements were mediated by an increase in capillary density and oxidative capacity in muscle biopsies. A meta-analysis of controlled trials involving exercise training found that such programs improve performance on the 6-minute walk test (6MWD), a key endpoint in most pivotal pharmaceutical trials in PAH and CTEPH, by 60.1 meters and

$\dot{V}O_{2\text{peak}}$ by 2.41 mL/kg/min.⁶⁹ For comparison, pharmaceutical trials in PAH improve the 6MWD on average by 31 meters.⁷⁰ Improvements in 6MWD are consistent regardless of the severity of impairment at baseline (i.e. similar improvements for patients in WHO functional class II, III, and IV at baseline) and across types of PH.⁷¹ Some of the improvements in exercise capacity and $\dot{V}O_{2\text{peak}}$ may be related to the effects of exercise training on hemodynamics. This was shown in a randomized trial of PAH and inoperable CTEPH patients that were already on stable PAH therapies for 2 months. After undergoing a 15-week training program, patients had a decrease in mPAP by 8mmHg, a decrease in pulmonary vascular resistance (PVR) by 2.1 Wood units, and an increase in cardiac of 0.5 L/min/m² compared to a control group.⁷² Performance during exercise training can be optimized by using supplemental oxygen during incremental WR exercise and constant load endurance exercise. Ulrich et al. performed a randomized sham-controlled cross-over trial of oxygen (FiO₂ 0.50) versus ambient air in PAH and inoperable CTEPH patients.⁷³ By diminishing the effects of arterial desaturation on chemoreceptor-induced hyperventilation, hyperoxia improved maximal work load by 19.7W and cycle endurance time by 11.2 minutes.

Exercise training programs might help PH patients by improving hemodynamics (cardiac index, mPAP and PVR), muscle function (strength and endurance), and may improve exercise capacity above and beyond pharmaceutical interventions.

Exercise programming recommendations

The key components of a supervised exercise program for PH patients are shown in Table 2.⁷⁴ Regular endurance training, strength training, and respiratory muscle training should be performed in addition to activities of daily living. Respiratory training may include breathing techniques, stretching exercises, inspiratory threshold loading devices and activities such as yoga.^{75,76}

Conclusion

PH patients demonstrate numerous indicators of decompensated cardiopulmonary physiology during exercise which can help point clinicians towards a diagnosis of PH. Specifically, the presence of high \dot{V}_E/\dot{V}_{CO_2} with a low $P_{ET}CO_2$ during CPET in a patient with unexplained dyspnea should prompt consideration of pulmonary vascular disease in the differential diagnosis and further diagnostic investigations. CPET is also well established for assessing the degree of exercise intolerance and dyspnea, providing important prognostic information for patients with PAH and CTEPH. Furthermore, with exercise training deemed safe, feasible, and several clinical trials using exercise variables as primary efficacy outcomes, the emerging field of research examining the therapeutic benefits of exercise training in PH merits additional consideration. Future clinical trials are needed to evaluate the efficacy of exercise programs focusing on light-intensity endurance, strength, and respiratory training.

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Tables

Table 1.

Groupings of the different classes of pulmonary hypertension (PH).

PH Classification	Description
Group 1	Pulmonary arterial hypertension
Group 2	PH due to left-sided heart disease
Group 3	PH due to lung diseases and/or chronic hypoxia
Group 4	Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
Group 5	PH with unclear and/or multifactorial mechanisms

Note. PH = pulmonary hypertension.

Table 2.

Recommendations for supervised exercise programming in patients with pulmonary hypertension.

Exercise Modality	Frequency of exercise (sessions per week)	Duration per session (min)	Intensity	Additional comment
Endurance	2-3	10-25	60-80% of symptom-free capacity	Low intensity interval exercise recommended (e.g. low workloads for 30s followed by higher workload for 1 min)
Strength training	1-2	15-30	4-5/10 on Borg scale (somewhat strong/strong)	Strength devices or dumbbells, single muscle groups (e.g. quadriceps leg extensions), 1-2 sets. Avoid complex, multiple muscle group exercises (e.g. squats).
Respiratory muscle training	5-7	10-15	-	Specific techniques, stretching exercises for respiration-related muscles, body perception improvement, yoga breathing techniques
Activities of daily living	Daily	Whenever possible	Low intensity	Walking, cycling, gardening, stairs.

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Figure Legends

Figure 1. Pathophysiology and Mechanisms of Exercise Intolerance in Pulmonary Hypertension.

Pulmonary vascular obstruction results in high ventilation to perfusion ratios, impaired cardiac output and can result in hypoxemia due to right to left shunting through a patent foramen ovale. Inefficient ventilation proposes high ventilatory demand, high V_E/V_{CO_2} and V_D/V_T and low $P_{et}CO_2$. Cardiac limitation and peripheral muscle abnormalities result in a low anaerobic threshold, early onset lactic acidosis and increased V_{CO_2} , which provide further stimulation for excessive ventilation. Ventilatory mechanical constraints on tidal volume expansion also contribute to dyspnea during exercise.

Abbreviations: V/Q = ventilation to perfusion ratio; RV = right ventricle; LV = left ventricle; V_E = minute ventilation; V_E/V_{CO_2} = ratio of minute ventilation to carbon dioxide production; $P_{et}CO_2$ = end-tidal pressure of carbon dioxide; V_D/V_T = dead space to tidal volume fraction; VO_2 = oxygen consumption; WR = work rate; O_2 pulse = VO_2 to heart rate ratio; V_{CO_2} = carbon dioxide production; PvO_2 = venous pressure of oxygen; PaO_2 = arterial partial pressure of oxygen; $PaCO_2$ = arterial partial pressure of carbon dioxide. This is an original figure, no permission is required.

Figure 2. Comparison of oxygen consumption ($V'O_2$) to work rate (WR) relationships.

A normal individual with peak VO_2 of 97% has a VO_2/WR slope of 10.8 mL per Watt. A patient with pulmonary arterial hypertension (PAH, pulmonary vascular resistance 9.3 Wood units) and a preserved cardiac index ($CI = 2.7$ L.min.m⁻²) and moderately reduced peak VO_2 of 67% predicted has a borderline reduction in the VO_2/WR slope of 9.4 mL per Watt. The patient with

PAH and severe reduction in peak VO_2 (39% predicted) demonstrates a reduced VO_2/WR slope of 5.7 mL per Watt. Note that the difference in y-intercept (VO_2) at WR of 0 Watts is largely related to variability in body mass between these individuals.

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Figure 3:

Exertional dyspnea intensity as measured by Borg score is displayed in response to a) increasing work rate (WR) and b) increasing minute ventilation (V_E) during symptom limited cardiopulmonary exercise testing in 25 patients with pulmonary arterial hypertension (PAH) and 10 healthy control subjects. *: $p < 0.05$, PAH versus health control at rest and standardized exercise work-rates (20W and 60W) and peak exercise.

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Figure 4:

Maximal and tidal flow-volume loops (averaged data) are shown during cardiopulmonary exercise testing in patients with pulmonary arterial hypertension (PAH) who a) develop dynamic hyperinflation (PAH-H $n=15$) and b) do not develop hyperinflation (PAH-NH, $n=10$). Tidal flow-volume loops provided are at rest, early exercise (20W), late exercise (60W) and peak exercise. Note the significant decrease in dynamic inspiratory capacity and increase in end-

expiratory lung volume in PAH-H in comparison to PAH-NH. Reproduced with permission of the © ERS 2018. From: Laveneziana P, Garcia G, Joureau B, et al. Dynamic respiratory mechanics and exertional dyspnoea in pulmonary arterial hypertension. *Eur Respir J*. 2013;41(3):578-587.

Figure 5:

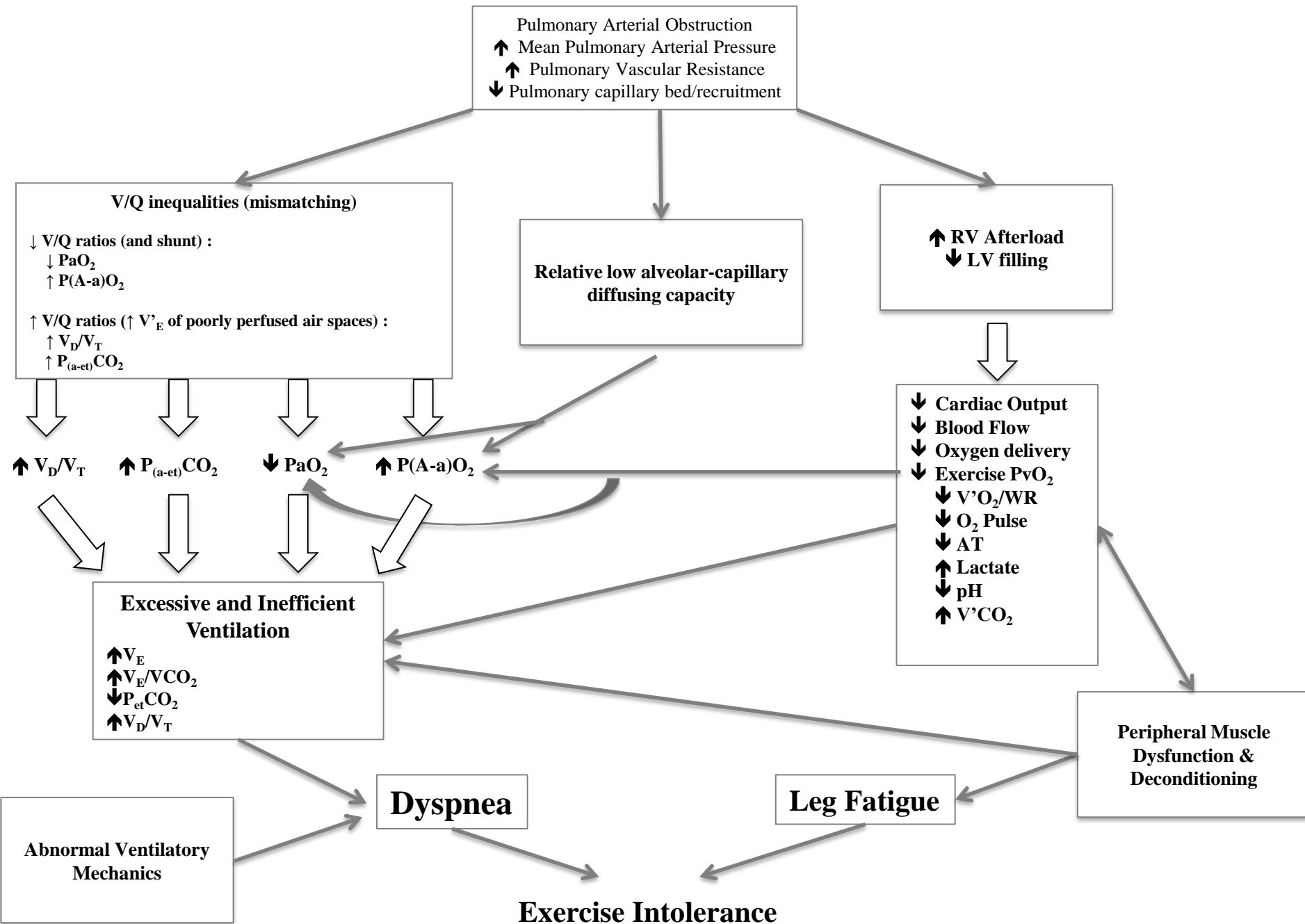
- A) Ventilation (V_E) plotted against CO_2 output (VCO_2) for patients with mild (circles) pulmonary arterial hypertension (PAH), moderate PAH (solid squares), and chronic thromboembolic pulmonary hypertension (CTEPH, triangles). The dashed line represents the upper limit of normal. Note that in the patient with mild PAH, the V_E/VCO_2 slope is only mildly abnormal (V_E/VCO_2 slope = 30), whereas the patient with moderate PAH and severe CTEPH have significantly elevated V_E/VCO_2 slopes of 84 and 115, respectively.
- B) End-tidal PCO_2 ($P_{et}CO_2$) plotted against time for the same patients in (a). Note that the patient with mild PAH (circles) exhibits a slight increase in $P_{et}CO_2$ during early exercise, similar to the predicted normal response (dashed line). The patient with moderate PAH exhibits a flat $P_{et}CO_2$ during early exercise with a terminal decline coinciding with hyperventilation after the anaerobic threshold. The patient with severe CTEPH demonstrates a progressive decrease in $P_{et}CO_2$ characteristic of severe pulmonary vascular disease.

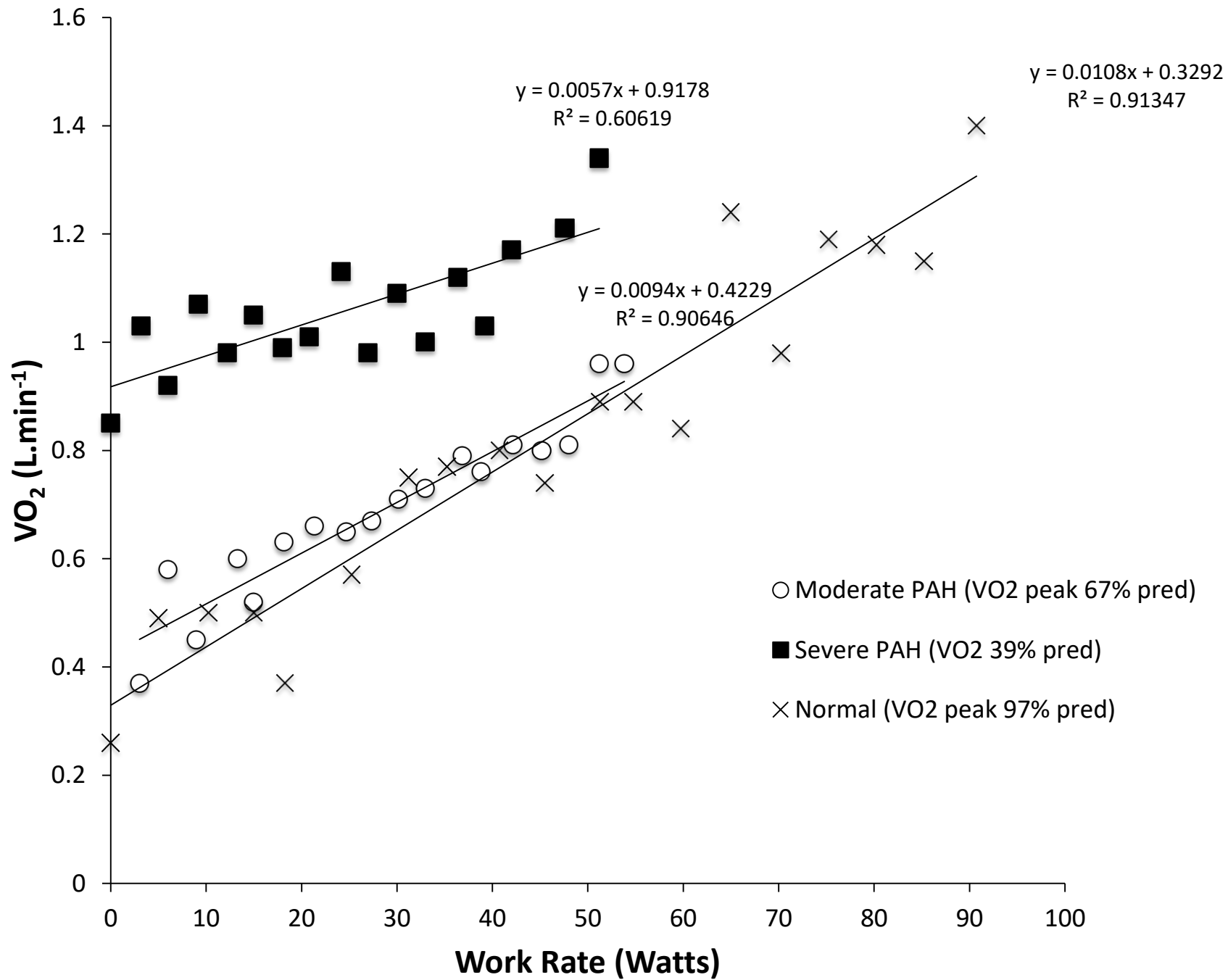
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Figure 6: Gas exchange abnormalities for a patient with pulmonary arterial hypertension (PAH).

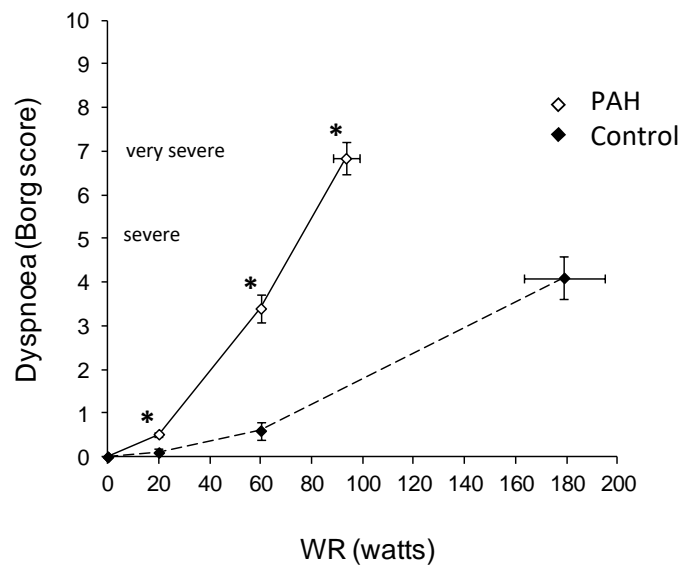
Dashed lines represent predicted normal responses. Note the excessive ventilation for a given VO_2 (upper left panel) with high physiologic dead space (V_D/V_T) at rest and throughout exercise (lower left panel). The arterial CO_2 pressure (PaCO_2) is low at rest and decreases early during exercise to a greater extent than in a normal individual (upper right panel). The arterial oxygen pressure (PaO_2) decreases abnormally during exercise despite a normal increase in alveolar oxygen pressure (PAO_2), resulting in a wide and increasing alveolar-arterial O_2 difference at peak exercise (lower right panel). Reproduced with permission of the © ERS 2018. From: Weatherald J, Laveneziana P. Patterns of cardiopulmonary response to exercise in pulmonary vascular diseases. *Eur Respir Monogr.* 2018;80:160-174.

Exercise intolerance in Pulmonary Vascular Diseases





a)



b)

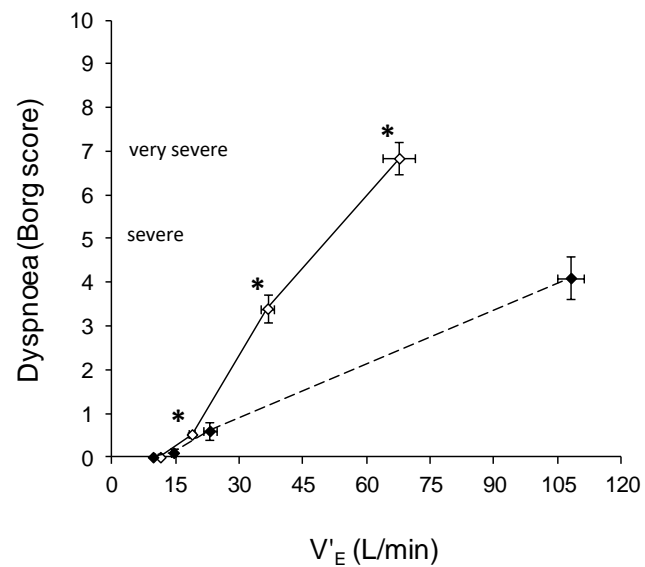
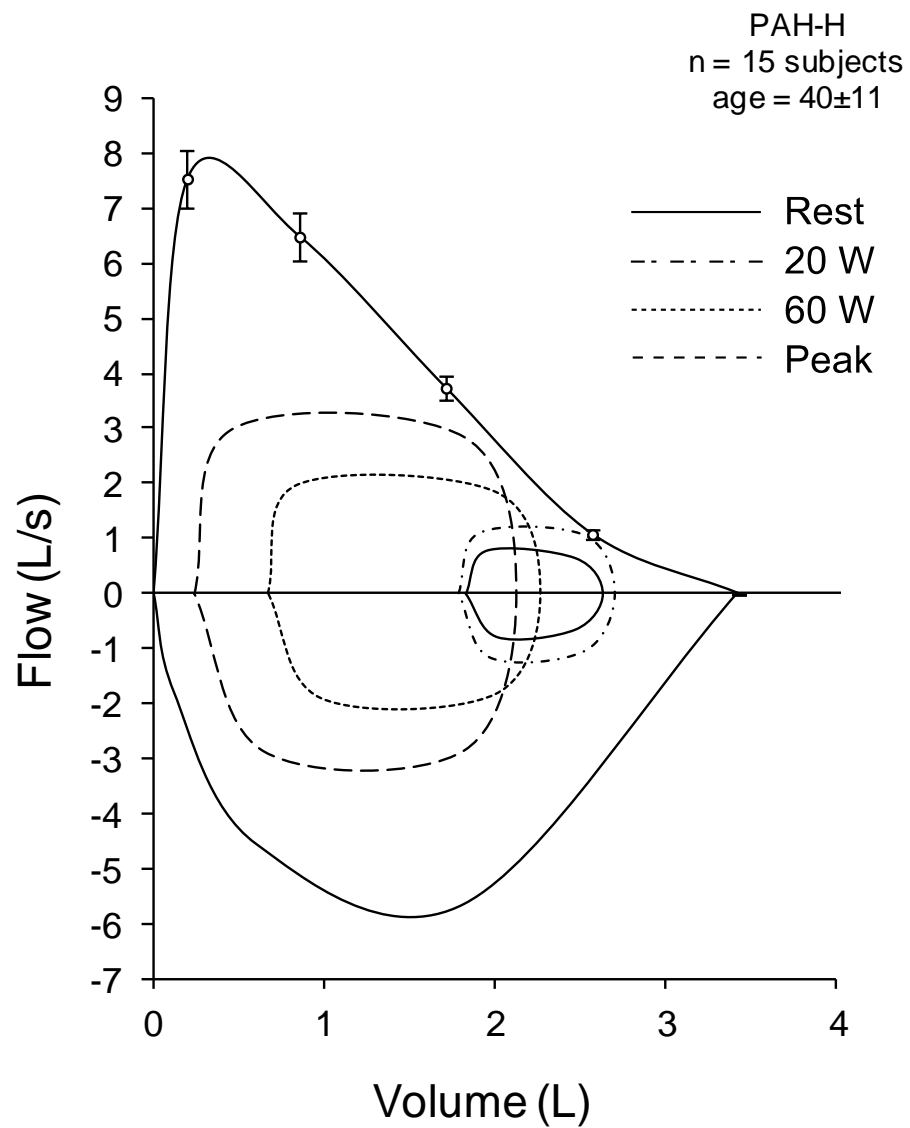
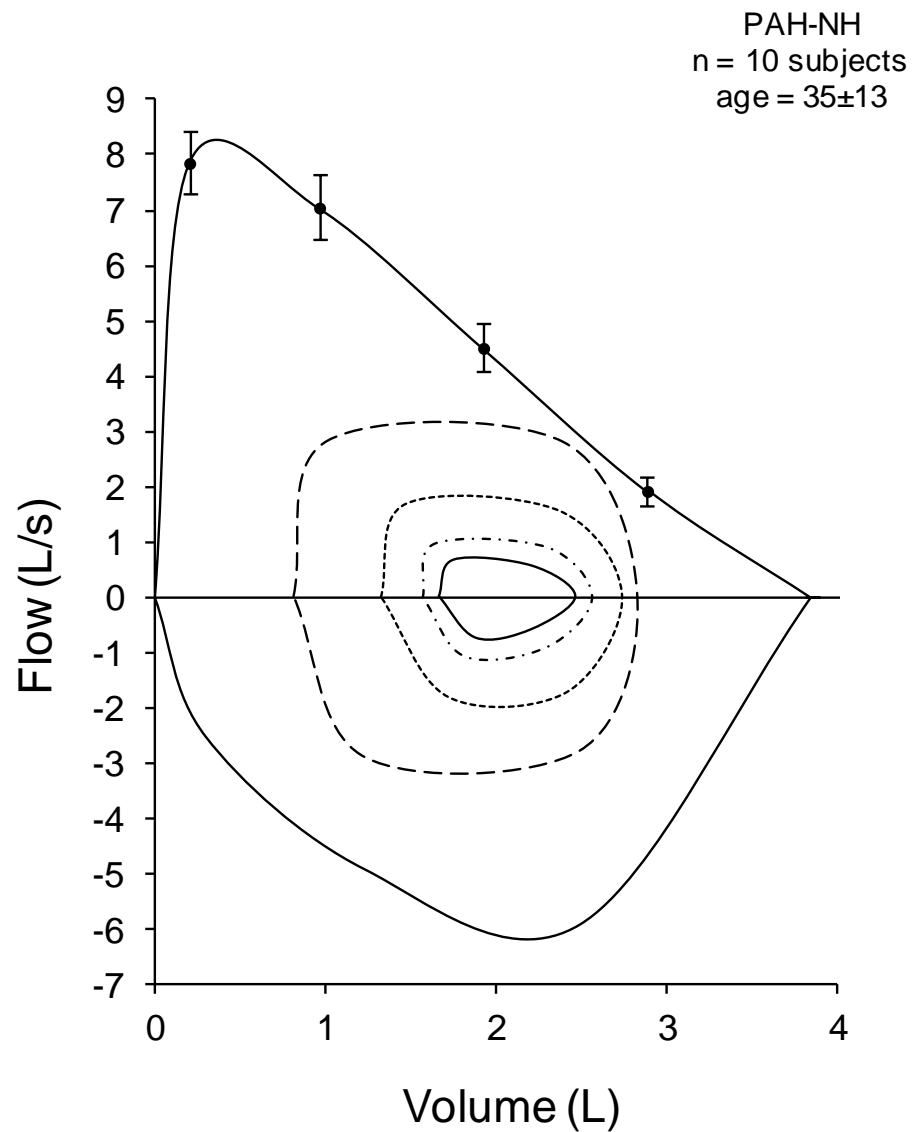


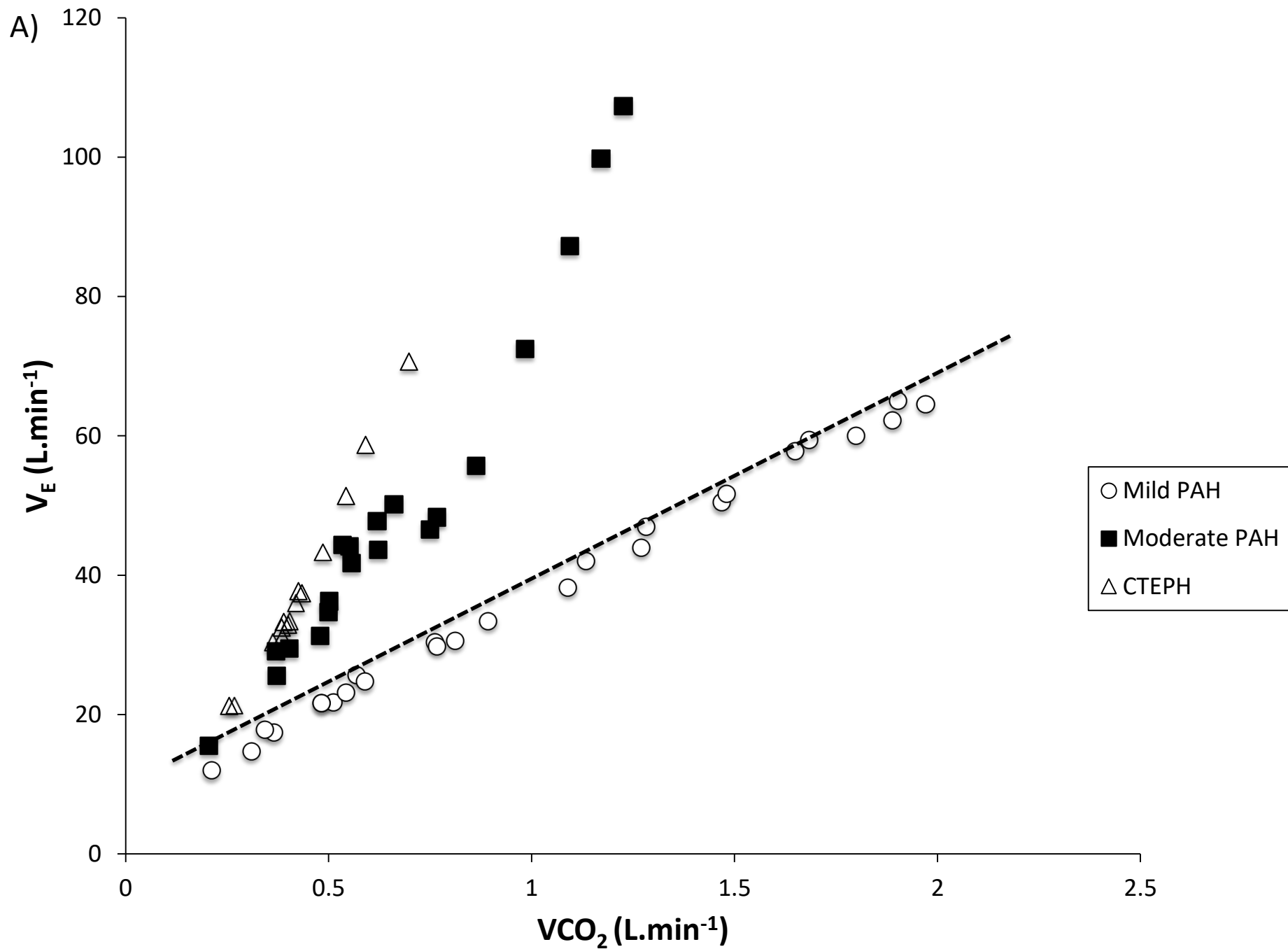
Figure 3

a)



b)





B)

