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Exercise and PH: Nuts, Bolts, and Clinical Uses

Program Description

The mission of *Advances in Pulmonary Hypertension* is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension. The 2018 Nice revision of the World Health Organization Classification serves as a guide to categories of pulmonary hypertension addressed in *Advances in Pulmonary Hypertension*. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group 2, pulmonary venous hypertension; Group 3, associated with chronic lung disease and/or hypoxemia; Group 4, PH due to pulmonary artery obstructions; Group 5, miscellaneous) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

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Advances in Pulmonary Hypertension is directed to cardiologists, pulmonologists, rheumatologists, pediatricians, internists, and other health care professionals involved in the treatment of patients with PH.

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of *Advances in PH* is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
- Letters to the Editor
- Clinical case studies

Submitted manuscripts are reviewed by the Editorial Board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision-making.

CONTENTS

Advances in Pulmonary Hypertension's Web Platform

*Advances in Pulmonary Hypertensio*n is available at www.AdvancesinPH.org. This site offers enhanced capabilities including a dedicated DOI and cross-referencing potential, as well as other features valuable to practitioners, researchers, and educators. Registration is recommended to access all site features and benefits.

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EDITOR'S MEMO

Welcome back to *Advances in Pulmonary Hypertension* Volume 18! First and foremost, I would like to thank everyone involved for making the transition to our now online journal. Michael Gray and Rebecca Aune from the PHA have been invaluable leaders in this charge to not only make this a smooth transition, but also to improve the quality of our journal. Thank you to Clarissa Nemeth from Allen Press who has joined the *Advances* team as the Managing Editor. And to all of the editorial board members and guest editors, thank you for being instrumental, submitting topic ideas and innovative ways to make the online journal a hit. The response to first online issue (Vol 18, No. 1) has been great and we are looking forward to new ideas, additions, and improvements in the coming issues. Congratulations to all.

In this issue, *Advances* examines the role of exercise in pulmonary hypertension (PH). Drs Ron Oudiz and Harrison (Hap) Farber proposed this subject a year ago when realizing the lack of a recent solid update on this important topic in PH. As guest editor, Dr Oudiz took on this challenging issue and he has assembled a group of international experts to discuss multiple topics. The issue he and the authors have together created is an outstanding educational resource and the most up-to-date reference on this subject.

This *Advances* issue includes multiple aspects of exercise in association with PH. The three main manuscripts as well as the regular sections of the journal tease out the most important areas to discuss. In the first article, Dr Daniel Dumitescu (Germany) and Dr Ron Oudiz (US) review the pathophysiological mechanisms that are involved with exercise intolerance in pulmonary arterial hypertension (PAH), and the relevance for clinical practice and future outcomes. In the second article, Drs Franz Rischard and Barry Borlaug from the United States update us on how exercise testing (all types) is performed and the significance the results hold for our patients. In the third article, Drs Andrew Peacock and Martin Johnson (UK) discuss the important role exercise has for our patients.

The round table discussion is an important dialogue between Drs Aaron Waxman, Robert Naeije, and Ron Oudiz. They exam multiple areas of the topic for an up-to-date world-class review. In the Ask the Expert section, Dr Lana Melendres-Groves (US) reveals how her center approaches exercise and relays her exercise prescription for her patients. A. Marlene Pirfo and Dr Edward Chen (US) address the practical aspects of pulmonary rehabilitation for patients in the PH Professional Network section of the journal. Finally, although not related to exercise, Drs Abhinav Gupta, Christine Dillingham, Harrison Farber, and Mary Jo Farmer (US) present an important case and review of PH related to an arteriovenous fistula.

I know you will enjoy and learn so much from this issue of *Advances*. It will no doubt be a valuable resource that provides current reflections by international experts on the role of exercise in PH patients.

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GUEST EDITOR'S MEMO

As guest editor for *Advances* this quarter, I had the great pleasure of getting together worldwide experts to create an all-things-exercise issue. This international issue provides major updates covering exercise in diagnosis, prognosis, and intervention (rehabilitative exercise) for pulmonary hypertension (PH) patients. Dr Daniel Dumitrescu (Germany) covers the physiology behind exercise and PH. Drs Franz Rischard and Barry Borlaug (US) cover the technical aspects of how exercise testing is performed. Drs Andrew Peacock and Martin Johnson (UK) describe the role of exercise in PH. And Dr Lana Melendres-Groves (US) does a nice Ask the Expert piece covering how she approaches her "prescription" for exercise. In the PH Professional Network (PHPN) corner, A. Marlene Pirfo and Dr Edward Chen (US) address the practical aspects of pulmonary rehabilitation for patients.

Searching the online content for *Advances*, I found the last roundtable on exercise was published 10 years ago! So Drs Aaron Waxman (US) and Robert Naeije (Belgium) and I got together for a 45-minute roundtable and chatted about…well, you guessed it: exercise.

I hope you enjoy this issue as much as I enjoyed participating in it.

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Exercise Pathophysiology in Pulmonary Arterial Hypertension—The Physiologic Explanation for Why Pulmonary Arterial Hypertension Does What It Does

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Pulmonary arterial hypertension (PAH) is a chronic disease that is associated with a significant and progressive limitation of exercise tolerance. The pathophysiological mechanisms of exercise intolerance during exercise are complex, multifactorial, and in fact not limited to the pulmonary circulation and the right ventricle. Disturbance of autonomic nervous function leads to an enhanced chemosensitivity, as well as respiratory and peripheral muscle weakness, and systemic endothelial dysfunction, which together play important roles in PAH pathophysiology and symptomatology. This article is focused on the different pathophysiological mechanisms of exercise intolerance in PAH, their interactions, and their relevance for clinical practice.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a primary disease of the pulmonary vasculature, which is caused by primary structural changes of the pulmonary arteries. These changes lead to an elevation of pressure and resistance in the precapillary part of the pulmonary vasculature, and are therefore characterized by a chronic increase in right ventricular afterload (increased pulmonary vascular resistance)[1] and loss of pulmonary vascular capacitance,[2] potentially leading to right ventricular failure and death. Additionally, the efficiency of alveolar gas exchange of oxygen and carbon dioxide (CO_2) is significantly impaired. Exercise limitation and dyspnea are among the most frequent and distressing symptoms of PAH.[3] In most cases, exercise capacity is limited by a circulatory (heart and/or blood vessel) exhaustion, and not by a lack of breathing (airway) reserve. In addition, autonomic nervous dysfunction leading to an enhanced chemosensitivity, respiratory and peripheral muscle weakness, and systemic endothelial dysfunction play additional and perhaps equally important roles in PAH pathophysiology and symptomatology.

This article focuses on the many pathophysiological mechanisms of exercise intolerance in PAH, their interactions, and their relevance for clinical practice.

FUNCTIONAL AND METABOLIC CHANGES IN THE PULMONARY CIRCULATION DURING EXERCISE IN HEALTHY SUBJECTS

In contrast to the systemic circulation, the pulmonary circulation is a low-pressure and high-compliance system at rest and during exercise. While systolic blood pressure in the systemic circulation rises by about 0.33 mm Hg/W[4] during exercise in healthy subjects and reaches age-dependent peak values of 204 to 213 mm Hg in men and 173 to 192 mm Hg in women,[5] the pulmonary vasculature remains a low-pressure circuit even at an increased cardiac output in normal individuals. The increase in pulmonary arterial mean pressure (mPAP) during exercise is dependent on age and pulmonary blood flow; however, mPAP rarely exceeds 30 mm Hg in healthy subjects.[6] At progressing exercise levels and elevated cardiac output, a modest decrease in total pulmonary resistance and a very modest decrease in pulmonary vascular resistance can be observed.[7] The most recent definition of "exercise pulmonary hypertension" by the European Respiratory Society[7] is based on the relationship between mPAP and cardiac output. According to this reference, an abnormal hemodynamic response to exercise is defined by the presence of a resting mPAP below 25 mm Hg with an increase in mPAP to > 30 mm Hg during exercise, with total pulmonary resistance > 3 Wood units.

These physiological considerations suggest that in normal individuals, an increase in cardiac output must be associated with a significant pulmonary vasodilatation and an increase in the total pulmonary vascular cross-sectional area; in other words, with exercise, a significant recruitment of additional pulmonary vascular bed and thus recruitment of additional lung areas participating in gas exchange occurs.

Gas exchange during exercise is regulated by arterial CO_2 levels, reflecting acid-base balance.[8,9] Minute ventilation($\dot{V}E$) is closely and necessarily linked to CO_2 output ($\dot{V}CO_2$) during exercise. At the beginning of exercise, an improvement of ventilatory efficiency is the norm. The ratio of $\dot{V}E$ to $\dot{V}CO_2$ decreases, as venous CO_2 content excessively rises due to elevated exercise metabolism and—at the same time—CO_2 is more efficiently exhaled due to an improved perfusion and additional recruitment of alveolar areas. Nadir values are reached at higher levels of exercise, at or near the respiratory compensation point.[10] In general, the lowest $\dot{V}E/\dot{V}CO_2$ relationship during

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exercise is considered to be the preferred noninvasive method to estimate ventilatory efficiency.

Another important parameter reflecting ventilatory efficiency is the end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$). It is the highest alveolar PCO_2 during the respiratory cycle, approaching the mixed venous PCO_2.[11] An improved efficiency of pulmonary CO_2 elimination during incremental exercise intensity leads to an increase in $P_{ET}CO_2$, also reaching peak values at the respiratory compensation point. Both $P_{ET}CO_2$ and the $\dot{V}E/\dot{V}CO_2$ relationship reflect the matching of ventilation to perfusion during exercise.

EFFECT OF STRUCTURAL PULMONARY VASCULAR DAMAGE IN PRECAPILLARY PULMONARY HYPERTENSION

From a pathology point of view, PAH is an obstructive pulmonary panvasculopathy,[12] with loss and obstructive remodeling of the pulmonary vascular bed, leading to stiffening of large, lobar, or segmental pulmonary arteries. Additionally, distal arteries may be affected by medial hypertrophy or hyperplasia, fibrosis, and thrombotic or plexiform lesions.[13] Both the loss of small pulmonary arteries in the micrometer range and a reduced elasticity in the larger pulmonary arteries contribute to an elevation of pulmonary vascular resistance and the mPAP/cardiac output slope.[7] As a consequence, cardiac output cannot be increased during exercise without an excessive increase of pulmonary arterial pressure. If the right ventricle (RV) is not able to overcome this pressure elevation, pulmonary blood flow will not adequately increase during exercise in PAH patients, potentially leading to a relative underfilling of the left ventricle (LV), systemic hypotension, and reduced systemic perfusion. In addition, due to the loss of pulmonary vascular bed and diminished perfusion of ventilated lung areas seen in PAH, central venous CO_2 is eliminated with a higher minute ventilation compared to healthy subjects. Thus, there is an elevated ventilatory requirement for any given CO_2 output during exercise.

The pathophysiological changes of the pulmonary circulation during exercise in PAH are summarized in Figure 1.

Impairment of Pulmonary Blood Flow Increases With Exercise

Early works reported that cardiac output can increase 4- to 5-fold during exercise, while pulmonary arterial pressure may rise to about 2 to 3 times that of the resting value in healthy subjects.[14] More recent studies have consistently reported increases in pulmonary arterial pressure with a concomitant increase in cardiac output. As a result, total pulmonary resistance and pulmonary vascular resistance actually decrease (slightly) during exercise.[6,7,15] An mPAP/cardiac output slope (total pulmonary resistance) of more than 3 Wood units (240 dynes · sec · cm^{-5}) has been suggested for defining an abnormal hemodynamic response to exercise.[7]

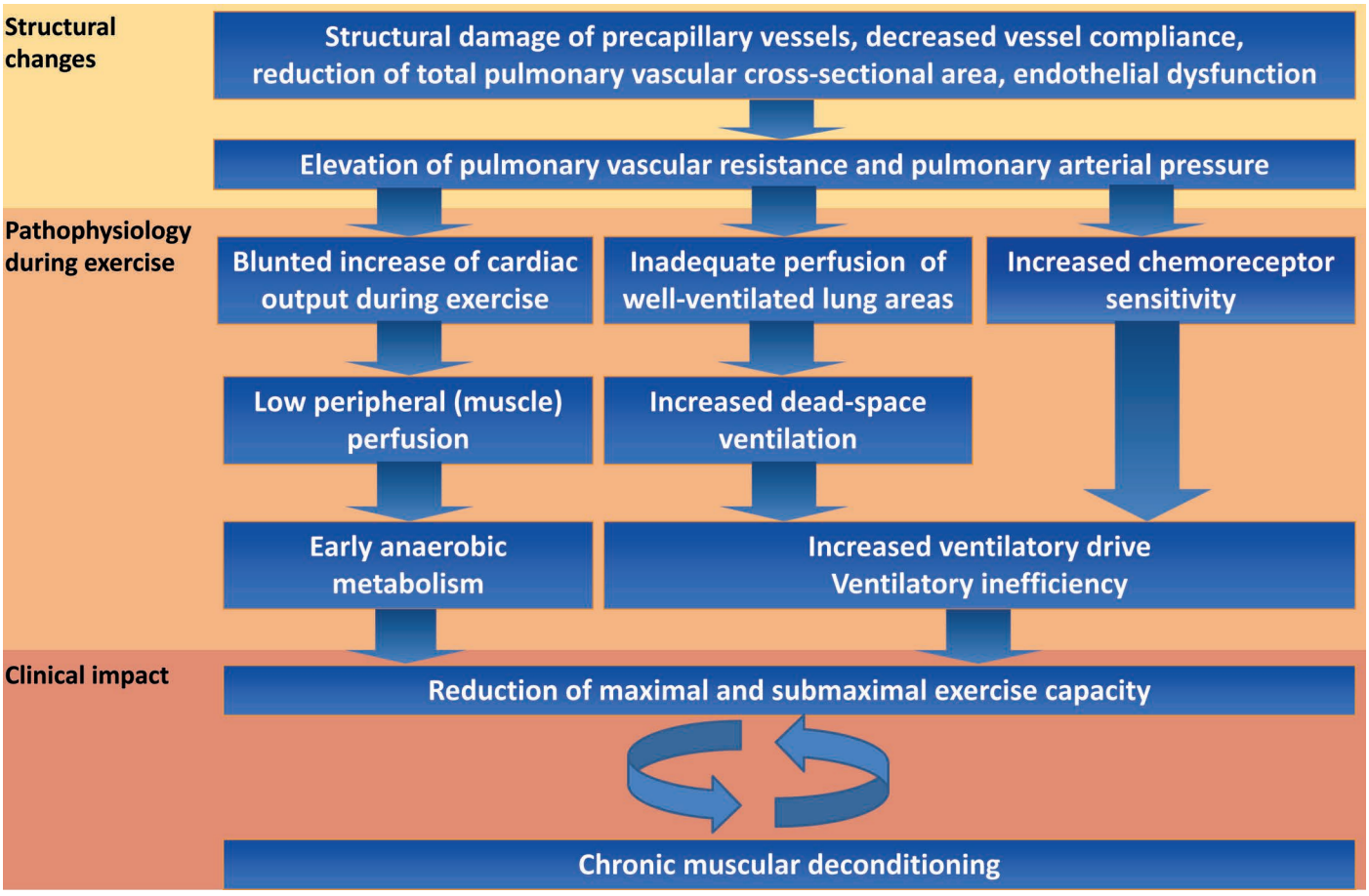

Figure 1: Overview of the pathophysiological mechanisms that may become relevant during exercise in pulmonary arterial hypertension patients.

Normal RV function is primarily determined by RV afterload. The RV ejection fraction is inversely correlated to pulmonary arterial pressure.[16] As the pulmonary circulation is normally a high-compliance and low-resistance system, the RV adapts to changes in volume rather than to changes in pressure.[17] With rising pulmonary vascular resistance, a decline in RV stroke volume is seen, which is significantly steeper than the decline in LV stroke volume.[18] Additionally, "ventricular interdependence" may become relevant. A flattening or a leftward shift (toward the LV) of the interventricular septum may reduce LV transmural filling pressure and/or restrict diastolic LV filling, potentially influencing systemic perfusion.[19] In summary, the increased circulatory demand during exercise, and the relatively sudden rise in pulmonary arterial pressure resulting, poses a hemodynamic challenge for the RV,[20] potentially impeding the requisite increase in cardiac output.

Based on these pathophysiological considerations, it is obvious that the increase of cardiac output needed in PAH patients during exercise requires significantly more energy than in normal individuals. Because the RV may not be able to adequately increase stroke volume during exercise, cardiac output is particularly dependent on the ability to increase heart rate in these patients.

Previous studies have consistently demonstrated that flow-related hemodynamic abnormalities have prognostic relevance. At rest, stroke volume index is an independent predictor of survival in patients with idiopathic, drug- or toxin-induced, or heritable PAH[21] and in patients with scleroderma-associated PAH.[22] Wensel et al[23] showed that peak systemic blood pressure during exercise, reflecting LV filling, was a strong and independent predictor of survival. In a cohort of patients with PAH and chronic thromboembolic pulmonary hypertension, the pressure-flow relationship predicted transplant-free survival and correlated with established markers of disease severity and outcome.[24] As exact measurement of cardiac output during exercise is technically demanding, data on the quantification of the cardiac output increase in PAH patients are limited. Immediately after modest exercise (30 W constant work rate), magnetic resonance imaging (MRI) data show that peak aortic blood flow is similar between PAH patients and matched controls, however with a significantly lower stroke volume and—as a compensation mechanism—a significantly steeper heart rate increase in PAH patients.[25] In that study, real-time cardiac MRI was able to unmask depleted contractile reserves. In contrast to healthy control subjects during acute normobaric hypoxia, PAH patients had a lower peak cardiac index, were not able to augment stroke volume index, and showed an impaired RV reserve, despite comparable resting function to controls.[26]

The Pulmonary Ventilation/Perfusion Relationship

Patients with PAH and other forms of relevant precapillary pulmonary vasculopathy, such as chronic thromboembolic pulmonary hypertension, hyperventilate at all metabolic states, potentially even during sleep.[23,27-29] Due to the nature of the disease, with lung areas that are normally ventilated but poorly perfused, these patients do not perform gas exchange with normal efficiency. Compared to healthy subjects, a significantly higher amount of minute ventilation is needed to eliminate any given amount of CO_2. As CO_2 levels are the major driver of ventilation during exercise,[8,9] inefficient CO_2 elimination must trigger an additional ventilatory drive. Early works showed preservation of matching of alveolar ventilation to perfusion, suggesting an active redistribution mechanism of alveolar ventilation as a compensation mechanism.[30] However, in most cases this compensation is not sufficient to achieve a normal, or physiological, $\dot{V}E/\dot{V}CO_2$ relationship during exercise. Unlike healthy subjects, this ventilatory inefficiency in PAH patients is evident by their inability to improve ventilatory efficiency during exercise; the $\dot{V}E/\dot{V}CO_2$ relationship is in fact elevated at rest, and *does not decrease* during exercise. Concomitantly, $P_{ET}CO_2$ is significantly reduced at rest, and *does not increase* during exercise in PAH patients. Patients with more advanced PAH may even show a continuous increase of the $\dot{V}E/\dot{V}CO_2$ relationship and a continuous decrease of $P_{ET}CO_2$ during exercise.[27,28]

Ventilatory inefficiency in terms of the $\dot{V}E/\dot{V}CO_2$ relationship and $P_{ET}CO_2$ may be considered for the differential diagnosis of ventilatory versus circulatory/pulmonary vascular limitation. A low ventilatory efficiency (high $\dot{V}E/\dot{V}CO_2$ relationship, low $P_{ET}CO_2$ at the anaerobic threshold), together with sufficient breathing reserve, hypocapnia, and a high positive gradient between arterial and end-tidal PCO_2 ($P_{(a\text{-}ET)}CO_2$) may indicate a significant pulmonary vascular component of exercise limitation.[31,32]

While elevated $\dot{V}E/\dot{V}CO_2$ relationships may be explained by reduced lung perfusion and an increase of dead space ventilation in the affected areas, *hypocapnia* demonstrates that there is an additional component of hyperventilation present and visible already at rest.[33] Recent studies have shown that autonomic nervous system disturbances may play an important role in ventilatory inefficiency, and that there may be an additional component of increased chemoreceptor sensitivity leading to hyperventilation in PAH.[34] Farina et al[35] demonstrated that ventilatory responses to brief periods of inspiratory hypoxia and steady-state hyperoxic hypercapnia in subjects with PAH were about twofold greater than in matched controls.[29,35] According to this study, hyperventilation in PAH is explained by a combination of increased dead space ventilation and an enhanced sensitivity of chemoreceptors.

Skeletal Muscle Dysfunction in PAH

The pathophysiology of exercise limitation in PAH is not limited to the RV, the pulmonary circulation, and the autonomic nervous system. Exercise intolerance in PAH is a complex phenomenon, additionally involving weakness of respiratory[36] and peripheral muscles.[37,38] Patients with significant chronic cardiopulmonary exercise limitations will undergo a process of progressive muscular deconditioning, affecting exercise capacity and quality of life. The mechanisms of muscle deconditioning are not yet completely understood. The dysfunction of sarcomers, the smallest

contractile unit in the muscle, may play a significant role in PAH.[39-41]

Specific medical PAH therapy alone has been shown to improve submaximal exercise tolerance reflected by an improvement in 6-minute walking distance. However, in several clinical trials with pulmonary vasodilator therapy for the treatment of PAH, peak oxygen uptake as an endpoint was negative.[42,43] Despite recognized limitations in methodology,[44] the results from these studies might indicate that *maximal* exercise tolerance (peak oxygen uptake) in PAH may only be significantly improved by a combination of medical therapy and supervised exercise training.

Systemic Endothelial Dysfunction in PAH

Patients with PAH have abnormal systemic vascular endothelial dysfunction, demonstrated by impaired flow-mediated dilation in the peripheral circulation,[45,46] likely mediated by reductions in endothelial-derived nitric oxide and prostaglandins[47,48] and adenosine,[49] as well as proinflammatory cytokines[50] and increased sympathetic nerve activity.[51] These abnormalities are associated with abnormal skeletal muscle structure and performance[52,53] and therefore likely contribute to the exercise impairment seen in PAH patients.

CONCLUSION

The pathophysiology of PAH during exercise is complex, as the interface between the lung, the pulmonary circulation, and the heart is affected by the disease. Exercise limitation is a multifactorial phenomenon. It is attributable, but not limited, to an impaired increase in cardiac output, a significant reduction in ventilatory efficiency and an increase in dead space ventilation, and enhanced chemosensitivity as well as a progressive weakness or deconditioning of respiratory and/or peripheral muscles. The noninvasive diagnostic evaluation of these mechanisms may be technically challenging in clinical practice, limiting their use for routine workup. Nevertheless, the knowledge of the pathophysiological mechanisms that limit exercise may be helpful for differential diagnosis and the serial follow-up of PAH patients as well as for the design of future clinical trials.

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Tools of the Trade: How Do You Perform and Interpret an Exercise Test?

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Background: Most pulmonary vascular disease (PVD) is poorly modifiable and incurable even with effective therapy. Therefore, adaptation to stress, the reserve of the cardiopulmonary system, is important for assessment of patient function and prognosis. Methods that assess the adaptation to stress, especially exercise, provide valuable insight into diagnosis, prognosis, and response to therapy.
Implications for Clinicians: We provide a comprehensive review of the indications, methodology, and interpretation, as well as practical information of the forms of provocative testing in PVD. We include 6-minute walk testing, noninvasive cardiopulmonary exercise testing (CPET), invasive CPET, and additional forms, including volume loading.
Conclusions: Through a clear understanding of the methodology in the assessment of PVD, the clinician can determine which of these "tools of the trade" are best suited to the individual patient and situation.

> "It's not the load that breaks you down, it's the way you carry it."
> *-Unknown*[a]

The capacity to respond to stress is one of the most important characteristics determining the ability of a human to thrive in everyday life. In patients with pulmonary vascular disease (PVD), reserve is compromised due to a number of factors, making response to stress an important discriminator with important implications for diagnosis, treatment, and prognosis. Practically speaking, exercise is the most commonly encountered stress in daily life, and exercise testing is accordingly the method of choice for inducing stress used in the evaluation of patients with or at risk for pulmonary hypertension (PH). Exercise is the most relevant to everyday stress and function for patients. Additional methods of "provocation," such as adrenergic stimulation, fluid loading, and inhaled nitric oxide, can be used to stress the cardiopulmonary system but are limited to differentiating left heart disease-associated PH (postcapillary) from other forms of PH (precapillary). Exercise testing in the field of PVD is used to:

- Assess prognosis;
- Determine the functional limitation, especially in complex disease (ie, multifactorial PH or dyspnea);
- Assist in the diagnosis of early disease and/or disease not apparent at rest (ie, exercise-associated or induced PH [EiPH] or heart failure with preserved ejection fraction [HFpEF]);
- Assessment of dyspnea of unknown origin (DUO).

There is also great interest in applying exercise stress responses in personalized medicine to describe complex PVD phenotypes and relate to omic markers.[1,2]

Methods of exercise assessment vary based upon equipment availability and physician expertise, and each modality has its own advantages and disadvantages (Table 1). The most common forms of exercise testing used in practice for the care of patients with PVD are the 6-minute walk (6MW) test and the noninvasive and invasive cardiopulmonary exercise tests (nCPET and iCPET). The purpose of this review is to provide a reader with a current clinical view of the indications, methods, and interpretation of exercise in PVD. Further, we attempted to give the reader practical suggestions should he or she wish to implement these methods in practice.

THE 6MW DISTANCE

Indications

The 6MW test is a well-studied method applied in the fields of cardiac and pulmonary medicine to estimate functional capacity[3] and prognosis.[4,5] A frequent implementation of the 6MW test in practice is to perform a baseline and follow-up test after intervention, such as pulmonary vaso-active therapy. The test is safe, reproducible, and requires relatively little training on the part of staff and interpreter (Table 1).

Methodology

The 6MW test is performed as a self-paced test of walking distance measured typically in feet or meters. Patients should be instructed not to exercise <2 hours before the test and take their usual medications. Vital signs are taken at rest before the test. Patients with oxygen saturation (SpO_2) at rest <85% should be administered supplemental oxygen (O_2),

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Note: Recommendations presented in this article are the views of the authors and are not necessarily endorsed by the Pulmonary Hypertension Association.

[a] This quote has been attributed to at least 3 public figures/writers. Because we are unable to verify authenticity, we have decided to designate the source as "unknown."

Table 1. Summary of Exercise Testing and Provocative Methods in the Assessment of Pulmonary Vascular Disease (PVD)

Test	Facility/staff utilization	Operator/interpreter experience and education	Advantages	Disadvantages
6MW	+	+	Inexpensive	Learning effect
			Validated to patient function	Cannot discriminate components of limitation[a]
			Safe	More effort dependent
			Reproducible	
			Prognostically relevant in some contexts[a]	
Noninvasive CPET	++	++	Effort better quantified	High level of experience needed
			Safe	Cannot discriminate well between PVH and PAH/DUO
			Components of limitation more easily defined than 6MWT	
			May be useful in to monitor therapeutic effect	
			May be useful to detect early disease in at-risk patients	
Invasive CPET	+++	+++	"Gold standard" method to determine cause of dyspnea and/or PH	High level of volume and experience needed for excellence
			Sensitive to all components of functional limitation	
			Provides additional prognostic information to resting hemodynamics	
Other, ie, iNO, fluid loading	++	++	Easily administered in the catheterization lab	Specific only to the evaluation of PAH versus PVH
			No or little additional staff support required	Limited data on cutoffs

6MW, 6-minute walk distance; CPET, cardiopulmonary exercise testing; iNO, inhaled nitric oxide; PVH, pulmonary venous hypertension; PAH, pulmonary arterial hypertension; DUO, dyspnea of unknown origin.

[a]Many patients with PVD have more than 1 potential etiology (ie, scleroderma with interstitial lung disease and PAH). The prognostic and functional implications of the 6MWD for these populations are unknown.

titrated to >90%. Patients who are on long-term O_2 should be studied on their typical O_2 flow rate. The subject should transport the O_2 device if possible, mimicking daily life. A forehead SpO_2 probe is advised for patients with Raynaud disease because digital capillary SpO_2 in these patients often does not reflect true arterial O_2 saturation. Patients are encouraged to walk as quickly as possible back and forth around cones placed ≥30 m apart in a straight hallway. Premeasured intervals (5-10 m) should be marked on the hallway. Standardized instructions and encouragement have been previously published.[6] A crash cart and staff with minimum basic life support certification should be available. Given that a 6MW test may elicit a near maximal O_2 consumption in patients with advanced PVD,[7] it has been recommended that similar contraindications and reasons for test termination be used for 6MW testing and CPET.[8] This has led to a departure from initial American Thoracic Society recommendations that pulse oximetry be monitored continuously and the test stopped if SpO_2 < 80%. We recommend that test administrators stand aside at the halfway mark (15 m) and observe the SpO_2 as the patient crosses twice per lap. Since there is a substantial learning effect in 6MW testing,[9] we recommend 2 tests be administered at baseline at least 24 hours apart and the higher result taken.

Interpretation

The validity of the 6MW distance (6MWD) as a clinically meaningful metric of patient function was assessed by Mathai et al.[3] They determined that the minimally important difference (MID) between 2 tests was 33 m to reflect an improvement in quality of life. This threshold is less often met when a patient is on combination PH therapy relative to monotherapy[10] or when the baseline walk distance is high.[11]

The use of the 6MW as a surrogate of outcome in pulmonary arterial hypertension (PAH) has met controversy in recent years. Although it has previously been used as the primary outcome measure in trials, Gabler et al found that changes in 6MWD did not correlate with hospitalization or survival.[12] Recent data from the SERAPHIN trial indicate that a threshold of >400 m after 6 months of therapy predicted substantially lower risk, but changes in 6MWD were not predictive.[13] Therefore, a treat-to-goal philosophy may be more impor-

tant than an incremental change if the 6MWD remains low. Composite scoring systems (such as European Respiratory Society [ERS] and Registry to Evaluate Early and Long-term PAH Disease Management [REVEAL]) have used the 6MWD among other factors to predict mortality,[14,15] which allow some flexibility and rationale to this treat-to-goal strategy. Conversely, patients experiencing a decline in 6MWD on therapy have a very poor survival.[16] A specific caveat regarding both the MID in distance and prognosis is that these studies were performed in patients with "pure" PAH. In clinical practice, many patients with PVD display characteristics of more than one etiology, and the applicability to these populations may be limited.

Practical Information

The Current Procedural Terminology (CPT) code (billing) used for 6MW testing is 94618.

6MWD Summary and Recommendations

- Given its practicality, we recommend the use of the 6MWD at baseline and 3 to 6 months follow-up in patients with "pure" PAH.
- New recommendations suggest monitoring SpO_2 during the test and stopping the subject of <80%.
- The 6MW test can be used to estimate a clinically important improvement in function but does not adequately elucidate the factors contributing to the improvement.
- A decline in 6MWD on therapy portends a poor prognosis, while improvement in 6MWD is favorably prognostic if a threshold >400M is reached.
- We encourage using the 6MWD with other factors in a treat-to-goal strategy using currently available clinical scoring systems (ERS and/or REVEAL).

THE NONINVASIVE CARDIOPULMONARY EXERCISE TEST

Indications

In contrast to the 6MW test, nCPET provides data regarding the pathophysiological mechanisms involved in PVD, including gas exchange, lung mechanics, indirect measures of cardiac function, and O_2 kinetics (uptake and utilization) during exercise. Therefore, nCPET is more useful in the differentiation of primary limiting factor(s) to exercise in patients with complex/multifactorial dyspnea.[17] nCPET is more informative regarding therapeutic responses if a baseline test is available.[18,19] nCPET is also useful in the prognostic evaluation of patients, especially when catheterization data[20] or echocardiography[21] are available. The advantages and disadvantages are summarized in Table 1.

Methodology

nCPET can be performed on a treadmill or cycle ergometer. Generally, we prefer the cycle in order to standardize work rates. Cycle ergometry also allows for greater stability for patients whom neuromuscular disease is a potential issue and can be stopped abruptly relative to treadmill exercise if needed. However, if the impact of body weight (obesity) on symptoms are desired, treadmill exercise is preferred, and peak $\dot{V}O_2$ values achieved are higher on treadmill. Additionally, if the patient has a pacemaker, cycle exercise may not trigger heart rate increase if triggered by an accelerometer. The patient should be monitored using electrocardiography and pulse oximetry, with exercise blood pressure assessed every 2 to 3 minutes. The metabolic cart itself consists of a pneumotachometer and gas analyzer which should be calibrated to known gas concentration before every study.

When selecting the type of exercise test (ie, ramp versus step), we typically use the 2-minute step protocol because it takes 1.5 to 2 minutes to achieve $\dot{V}O_2$ steady-state due the delay in O_2 uptake kinetics.[22] Prior to the test, the patient should be asked which activity brings about near maximal symptoms in 8 to 10 minutes. Patients reporting limiting symptoms walking from room to room, 1 flight of stairs, or >1 flight of stairs are administered a protocol with 10, 15, and 20 W step increments, respectively. Initially, patients undergo a 2-minute warmup without resistance at a pedal cadence of 60 rpm and are encouraged to maintain this cadence throughout the test. Exercise is terminated at subjective exhaustion, preferably when the patient meets a respiratory exchange ratio >1.0 (1.1 optimal), SpO_2 <80%, and/or staff feels it necessary for patient safety. We typically do at least 1 recovery stage at 2 minutes where expired gas analysis is continued. Supplemental O_2 is not used during CPET because this interferes with the $\dot{V}O_2$ assessment. In rare cases where exercise cannot be performed without supplemental O_2, a Douglas bag can be connected to a blender and a one-way valve in line with the inhalation port for supplemental O_2. nCPET is a safe test in practice when contraindications are followed.[23]

Interpretation

nCPET enables assessment of peak $\dot{V}O_2$, the "gold standard" measure of aerobic capacity. In addition, clues can be provided regarding the relative roles for abnormalities in gas exchange (low SpO_2), wasted ventilation (high $\dot{V}E/\dot{V}CO_2$), or abnormalities in the O_2 pulse ($\dot{V}O_2$/HR) which may reflect a limitation in right ventricular (RV) stroke volume, the ability to enhance arteriovenous difference during stress, or some combination of both. These patterns have been reviewed extensively, in both the PAH[24-26] and heart failure literature.[27]

nCPET has met with limited success in the diagnosis of PVD in patients with dyspnea of unknown origin (DUO). Relative to iCPET, its main limitation is its inability to measure cardiac and pulmonary pressure directly and thus to differentiate the presence or absence of PH, and then to determine whether it is caused by precapillary or postcapillary PH mechanisms (or both). Although nCPET can sometimes differentiate the pathophysiology of PAH from chronic obstructive pulmonary disease (COPD) or heart failure[28] and chronic thromboembolic pulmonary hypertension,[29] there exists significant overlap in many of these conditions. For example, in patients without resting abnormalities, such as detection of EiPH[30] and compensated HFpEF,[31] nCPET has limited success. Reddy et al[31] demonstrated that, in the differentiation of HFpEF

from patients with noncardiac dyspnea, there was significant overlap in peak O_2 consumption alone without invasive measures (Figure 1). nCPET may be useful diagnostically, however, only when targeted to specific at-risk populations such as scleroderma patients[32] or those in whom PH is suspected by echocardiography.[33]

Data from nCPET incrementally predicts mortality when added to resting hemodynamics.[20] However, using baseline data, nCPET adds marginal value when added to the prognostic capabilities of the 6MWD,[34] but nCPET may add incremental prognostic value in clinically stable patients on therapy. Badagliacca et al showed that nCPET peak $\dot{V}O_2$ > 15.8 mL/kg/min added incremental prognostic value to a change in cardiac index (0.4 L/min/m^2) in a PAH treatment cohort free of clinical worsening >12 months and most with a 6MW > 400 m.[35]

nCPET may also provide useful information in the assessment of response to therapy. Among PAH patients on background therapy, patients randomized to sildenafil demonstrated improvements in peak $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, and $\dot{V}O_2$/heart rate relative to those on placebo.[19] Further, survivors with PAH demonstrate greater changes in peak $\dot{V}O_2$ and $\dot{V}O_2$/HR relative to nonsurvivors on therapy.[18]

The validity and reproducibility of nCPET relies on operator and interpreter experience and case volumes and should ideally be performed at facilities where there is sufficient volume to warrant allocation of resources and training. For example, a study using nCPET as an outcome measure showed that there was only a high correlation between peak $\dot{V}O_2$ and 6MW at baseline in "experienced" centers.[36] As the study went on, the correlation increased in "nonexperienced" centers, indicating a learning effect.

Practical Information

Typically, nCPET is paired with resting spirometry for the assessment of airway flow volume loops at exercise and occasionally arterial blood gas analysis at maximal exercise. The typical CPT codes are available in the online supplement.

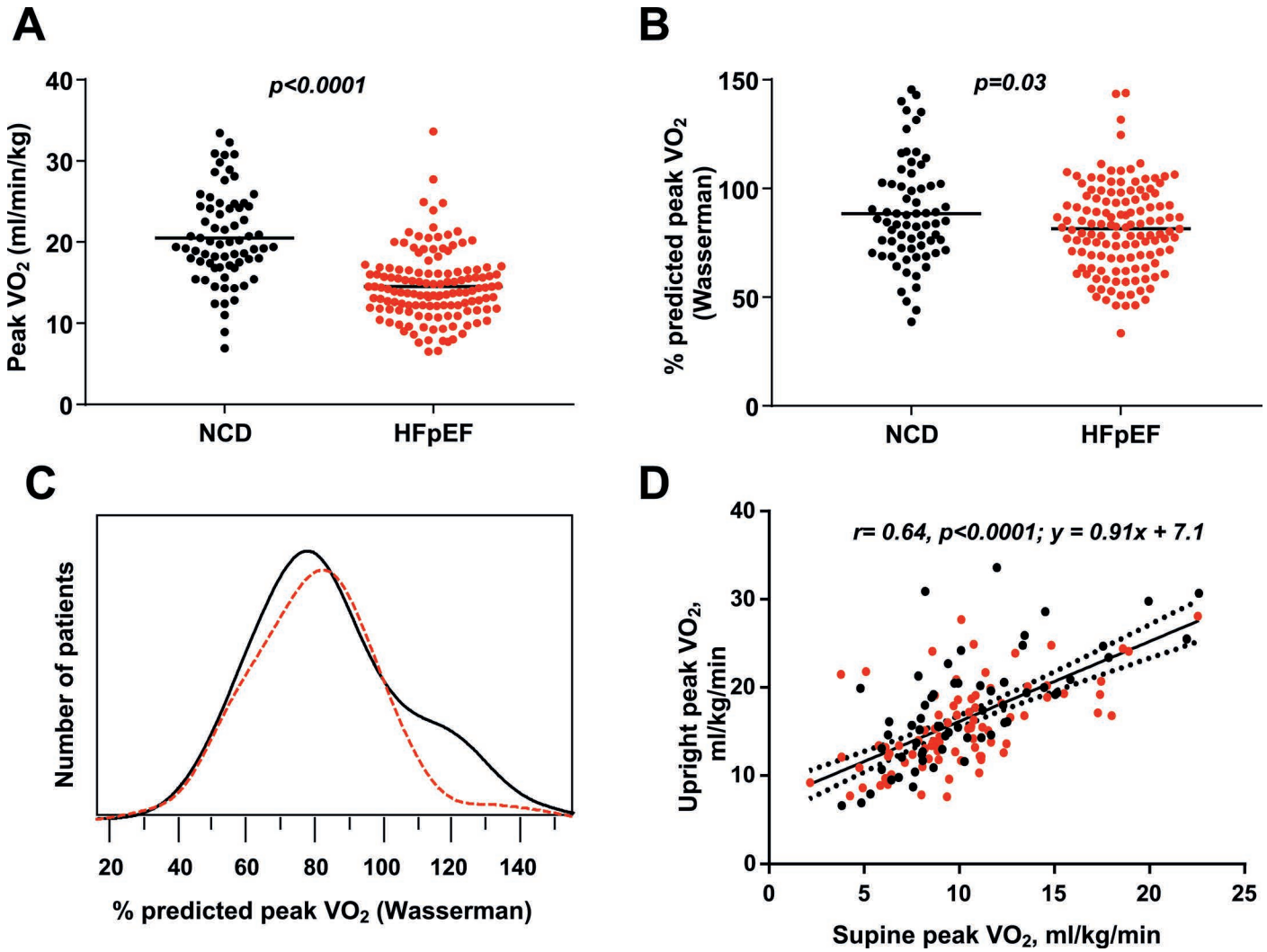

Figure 1: Percent predicted maximal oxygen consumption ($\dot{V}O_2$peak) among patients with unexplained dyspnea. Although there were significant (P = 0.03) differences in mean $\dot{V}O_2$peak between patients with noncardiac dyspnea (NCD) and heart failure with preserved ejection-fraction (HFpEF), there was significant overlap. This overlap limits the diagnostic discriminating ability of $\dot{V}O_2$peak in this population. Pulmonary capillary wedge pressure was the only accurate discriminator. Reproduced with permission.[30]

nCPET Summary and Recommendations

- nCPET is the "gold standard" test to assess aerobic capacity (peak $\dot{V}O_2$) and can provide insights into the main factors that limit aerobic capacity in patients with multifactorial dyspnea.
- nCPET has limited utility in the diagnosis of PVD in DUO due to its inability to measure cardiac and pulmonary pressures. It may be helpful in some at-risk populations as a screening tool.
- We generally recommend a cycle ergometry protocol using graded steps based upon physical capacity in daily life.
- nCPET may have utility when added to RV imaging in the prognosis of PVD.
- nCPET may be a useful tool in the assessment of therapeutic response.
- nCPET should be performed only at centers where there is a high enough volume to warrant the expertise needed for valid, reproducible testing.

INVASIVE CARDIOPULMONARY EXERCISE TESTING

Indications

iCPET is generally nCPET with a pulmonary artery (PA) catheter in place. At some sites, an arterial line is also placed routinely. In addition to nCPET, iCPET gives information regarding PA pressure, RV and left ventricular (LV) filling pressure, cardiac output (CO), and arteriovenous O_2 content difference ($Ca\text{-}vO_2$). These additional data make iCPET the ideal test to comprehensively evaluate complex multifactorial limitations such as the common heart failure and lung disease phenotypes. iCPET also provides the "gold standard" in the evaluation of patients with DUO.[37,38] iCPET offers promise in the assessment of prognosis for PAH[39] and HFpEF[40] when resting hemodynamics cannot. The advantages and disadvantages of iCPET are summarized in Table 1.

Methodology

The exercise protocols themselves for nCPET and iCPET are essentially the same. The test may be performed with upright or supine exercise, and details on the catheterization lab setup for both positions have been described.[37,38,41] Exercise catheterization has been done without a metabolic cart using a bicycle ergometer and thermodilution cardiac output (TCO) rather than direct Fick cardiac output calculated from measured $\dot{V}O_2$. We do not recommend this technique as TCO underestimates pulmonary blood flow at peak exercise[42] and because valuable ancillary expired gas data are not available (eg, $\dot{V}E/\dot{V}CO_2$, respiratory exchange ratio).

Supine iCPET allows the easier assessment by fluoroscopy and does not require the patient to move but is more difficult in the obese, patients with parenchymal lung disease where the lung volume loss is great, and in older adults. Upright exercise is more applicable to most everyday activity and is associated with less lung volume loss but requires frequent change in patient position and is difficult for fluoroscopy positioning.

Accurate transducer zeroing is imperative at all positions. In the supine position, the transducer is zeroed at ½ the anteroposterior dimension of the chest (Figure 2A).[43] This position should be maintained throughout exercise (Figure 2D). At the University of Arizona, exercise is typically done in the upright position in a fluoroscopy chair, which moves the patient from supine to upright. Zeroing is performed using fluoroscopy (Figure 2B), and exercise is done on a cycle ergometer mounted below the patient (Figure 2C).

Interpretation

Recent guidelines have not committed to the acceptance of criteria for PH with exercise due to uncertainties in age-related mean pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure (PCWP) cutoffs.[44] However, most guidelines acknowledge the importance of exercise data in the assessment of PVD. The European Respiratory Society recently released a statement proposing a mPAP > 30 mm Hg and a total pulmonary vascular resistance (tPVR = mPAP/CO) > 3 WU.[45]

PCWPs at rest of 15 mm Hg and 20 mm Hg at exercise (upright) or 25 mm Hg (supine) have typically been used to discriminate precapillary (lower values) from postcapillary (higher values) PH. Recent evidence suggests that evaluating PCWP with respect to the increase in CO may also hold value, with PCWP/CO slope > 2 mm Hg/L/min identifying patients at greater risk.[40] PCWP measurement has been a subject of controversy, where differences in computer-averaged (integrated pressure over time) versus end-expiratory measurements lead to errors in classification as precapillary or postcapillary PH.[46] As a general rule, PCWP averaged over the respiratory cycle is ~80% of what is measured at end expiration, due to the reduction in intravascular pressure caused by decreases in intrathoracic pressure during inspiration. When large respiratory swings are present, the computer-averaged PCWP tends to be more substantially lower than end-expiratory values. This phenomenon is particularly important in the obese[47] and patients with COPD and is augmented during exercise.[48] Because patients with obstructive lung disease frequently develop increasing positive end-expiratory pressure due to air trapping during exercise, this may falsely elevate end-expiratory pressures. Current guidelines recommend the use of end-expiratory pressure in the evaluation of left heart disease[49] and computer averaging in patients with parenchymal lung disease.[50] In patients that have wide respiratory variations, we find it is most helpful to report both values together to provide a complete picture (see right heart catheterization [RHC]) template, online supplement).

Specific pressure cutoffs for mPAP and PCWP are also sensitive to body position. When a patient is brought from supine to upright position, there is a commensurate drop in mPAP, PCWP, and CO due to the effects of gravity and reducing preload. Thus, current cutoffs for PH (mPAP > 20 mm Hg) and postcapillary PH (PCWP > 15 mm Hg)[44] are applicable only in the supine position. However, PVR seems unaffected by body position,[51] since changes in upstream, downstream pressures, and CO are similarly effected by gravity. If exercise is performed in the upright position, we recommend first obtaining data in the supine position.

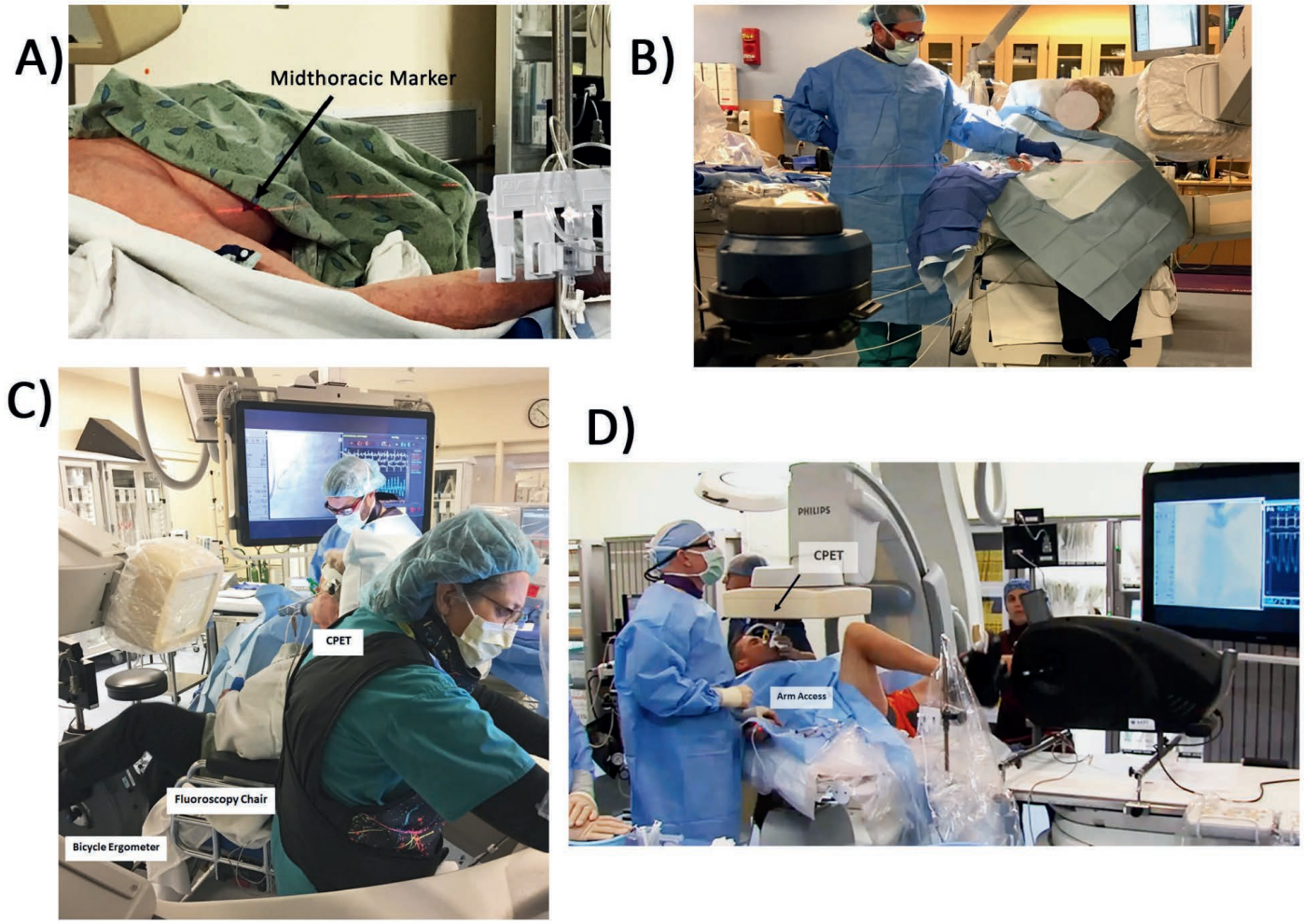

Figure 2: Catheterization lab setup for supine and upright invasive cardiopulmonary exercise testing. (**A**) Supine zeroing is done at the midthoracic level by measuring ½ the anteroposterior diameter of the chest. A laser is then used to bring the transducer stopcock to the midthoracic mark.[40] (**B**) Zeroing in the upright position is done by placing the tip of the pulmonary artery (PA) catheter in the atrium by fluoroscopy. Then scissors are placed at the tip of the PA catheter and a laser set at the scissors. Lastly, the transducer stopcock is placed at the laser. (**C**) Upright exercise is then undertaken with the use of a metabolic cart (CPET) and a bicycle ergometer mounted and wheeled below the patient. (**D**) Supine exercise is undertaken with the ergometer mounted to the catheterization table and the CPET at the head of the bed. The patients have explicitly given consent to be photographed for educational purposes. Photos courtesy of Dr Franz Rischard and Dr Michael Insel.

iCPET can be useful in the evaluation of DUO.[2,37,38] iCPET has been found to lead to overall earlier diagnosis and less testing in this population.[52] Many patients with HFpEF will have low LV filling pressures at rest requiring assessment with exercise.[37,38,53] iCPET is also required to confirm the diagnosis of EiPH.[54] Figure 3, left column, demonstrates the typical findings in an EiPH patient with normal resting hemodynamics but increased mPAP, PVR, $\dot{V}E/\dot{V}CO_2$, and reduced $\dot{V}O_2$ max and $\dot{V}O_2$/HR.

Given that most forms of PH are progressive despite therapy, the RV adaptation to chronic pressure overload is important in the assessment of prognosis. Patients who are able to mount a cardiac output response to exercise, termed RV contractile reserve or RVCR, despite increasing demands, show better adaptation and prognosis than those who cannot, even when resting hemodynamics are similar. In patients with HFpEF and PVD, RVCR is substantially reduced during exercise, and together with a reduction in left heart filling due to right heart overload, this leads to a dramatic impairment in cardiac output reserve and therefore exercise capacity.[55] In patients with PAH, a >20% increase in cardiac index from rest to exercise[39] or a mPAP/CO slope < 14 mm Hg/L/min[56] were more predictive of survival than 6MWD or resting hemodynamics. Figure 3, middle column, illustrates a patient with normal right atrial pressure (RAP) and CI at rest but poor RV contractile reserve. At exercise, there is severely increased mPAP, PVR, RAP, and $\dot{V}E/\dot{V}CO_2$ while stroke volume, $\dot{V}O_2$max, and $\dot{V}O_2$/HR are reduced. Particularly concerning is the dramatic rise in RAP with exercise versus compensated RV function seen with EiPH (Figure 3).[55]

Given that iCPET is a comprehensive evaluation of the factors that cause functional limitation, it is a useful tool in the assessment or phenotyping of patients with complex, multifactorial dyspnea. Figure 3, right column, shows iCPET data in a patient with scleroderma, HFpEF, and COPD. This patient shows both precapillary and postcapillary PH with increased

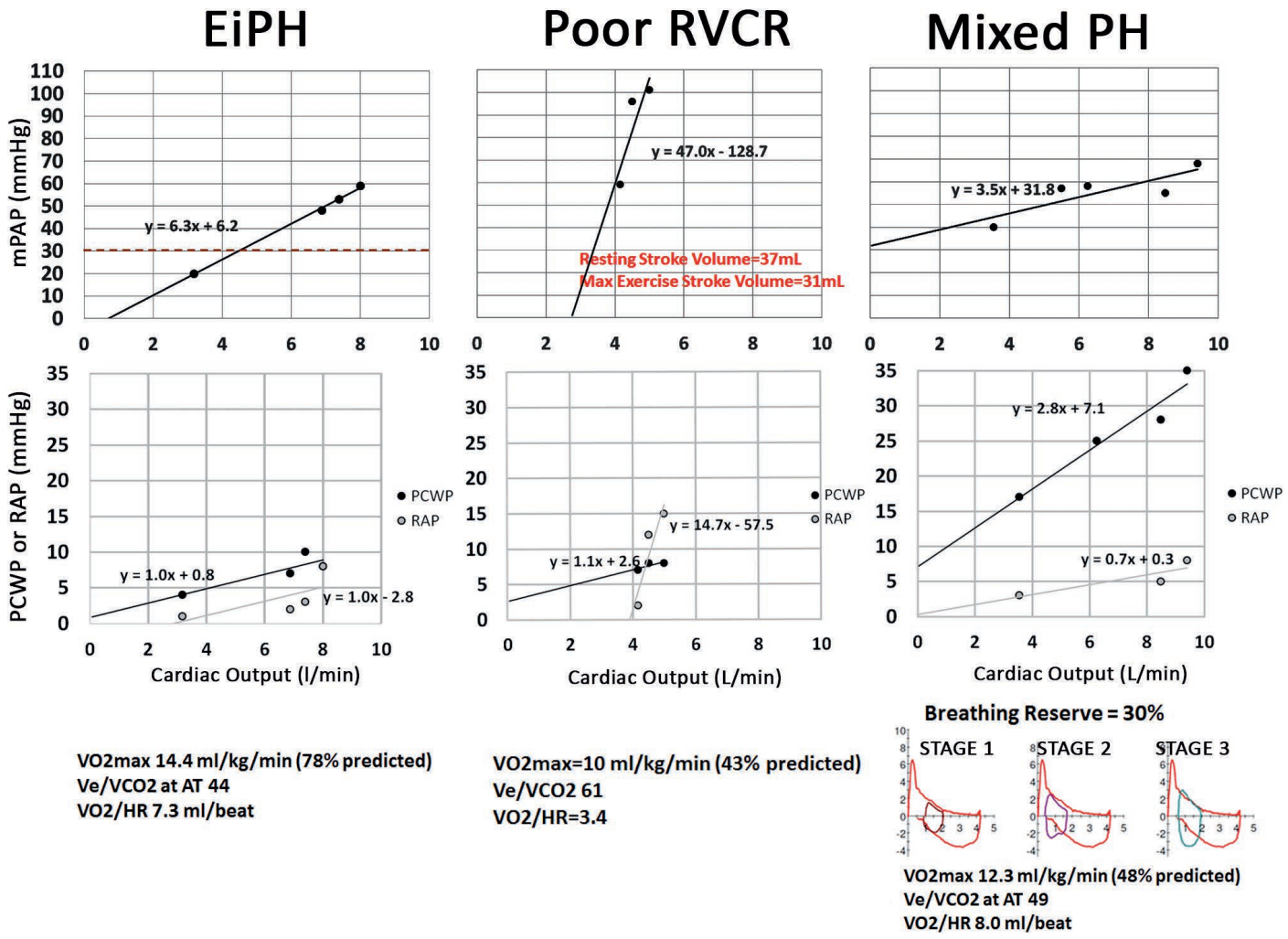

Figure 3: The utility of invasive cardiopulmonary exercise (iCPET) in the phenotyping of patients with pulmonary vascular disease. (**Left column**) Exercise-induced pulmonary hypertension (EiPH) is diagnosed by iCPET by mPAP at exercise >30 mm Hg (horizontal red line), a tPVR > 3 WU, normal PCWP, and abnormal $\dot{V}O_2$max and gas exchange ($\dot{V}E/\dot{V}CO_2$). (**Middle column**) Compensated resting PH with poor RV contractile reserve (RVCR) is characterized by normal resting CO and RAP but minimal increase of CO with exertion (1 L/min) and severely increased mPAP/CO (47 mm Hg/L/min) relative to EiPH ~5 L/min, and 6.3, respectively. Stroke volume actually falls with exertion, and severe PVD is manifest by significantly increased $\dot{V}E/\dot{V}CO_2$. (**Right column**) iCPET can also discriminate multiple causes of PVD in the same patient such as mixed PH. This patient with scleroderma and COPD has severe postcapillary PH with exertion (PCWP 35 mm Hg) with an additional precapillary component (PVR > 3 WU). There is limited breathing reserve and severe air trapping seen on airway flow volume loops by leftward migration to TLC. mPAP, mean pulmonary artery pressure; tPVR, total pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; $\dot{V}O_2$max, maximal oxygen consumption; $\dot{V}E/\dot{V}CO_2$, respiratory equivalent for carbon dioxide; RAP, right atrial pressure; COPD, chronic obstructive pulmonary disease; TLC, total lung capacity.

mPAP and PCWP relative to CO. There is also reduced breathing reserve and air trapping on airway flow volume loops (bottom right) indicative of COPD. Treatment was directed to both COPD and HFpEF in this patient. This strategy may be useful in phenotyping complex patients from a personalized medicine perspective[2,57] and has been adopted by the Pulmonary Vascular Phenomics Program (PVDOMICS).[1]

Practical Information

iCPET requires specific equipment and expertise and is currently best performed in high-volume centers with these capabilities. A description of the CPT codes we use for these procedures and an example procedure template is available in the online supplement.

Summary and Recommendations

- iCPET is the "gold standard" test to enable phenotyping of complex dyspnea and DUO.
- iCPET provides additional prognostic information to resting hemodynamics data regarding RV adaptation during stress.
- iCPET may be performed supine or upright, but resting supine measurements should be performed at diagnosis for all patients.
- We attempt to simulate a similar exercise protocol to nCPET in the lab.
- We recommend using either an exercise PCWP at end expiration of 25 mm Hg (supine), or a PCWP cutoff of 2 mm Hg/L/min to define postcapillary PH.
- Interpretation of waveforms in obese patients and patients with obstructive lung disease is challenging. Reporting of both end

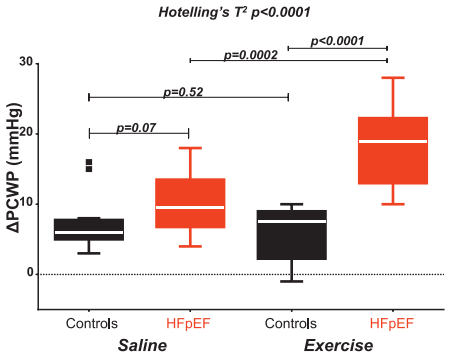

Figure 4: Differential effects of fluid loading versus exercise on pulmonary capillary wedge pressure (PCWP) in control patients versus heart failure with preserved ejection fraction (HFpEF). Although fluid loading and exercise show a similar change in controls, exercise showed a greater change in HFpEF patients. Therefore, exercise may be a more sensitive test for the discovery of HFpEF. Reproduced with permission.[58]

expiratory and mean of the respiratory cycle values is optimal.

- iCPET requires significant training, education, and staff resource utilization to maintain valid reproducible data.

ADDITIONAL METHODS OF PROVOCATION IN PVD

Because exercise equipment is not universally available in catheterization laboratories, additional provocative maneuvers have been applied. Arm exercise may be performed without the need for cycle ergometry, but hemodynamic changes induced are much less substantial when compared to leg ergometry.[37] Saline loading provides an isolated "preload stress" that may be useful to elicit occult abnormalities in LV diastolic dysfunction.[5] However, like arm exercise, the hemodynamic changes elicited by saline loading alone are much less dramatic than what is observed with the loading changes and tachycardia of cycle ergometry, and the sensitivity and specificity are accordingly lower (Figure 4).[59] A cutpoint of 18 mm Hg defining abnormal PCWP with saline loading has been proposed based upon normal data[60] but has not yet been rigorously validated. Exercise is associated with an increase in sympathetic tone, suggesting a potential role for catecholamine stimulation as with dobutamine. However, isolated β-adrenergic stimulation may have muted effects on pulmonary hemodynamics because improvements in lusitropy and pulmonary vasodilation or flow-related recruitment may cancel out the tendency to increase PA pressure in response to higher CO.[61] Therefore, adrenergic stimulation is rarely used as a provocative maneuver in the evaluation of PVD.

CONCLUSIONS AND FUTURE DIRECTIONS

Patients with PVD of all forms share limitations in cardiac and vascular reserve which are frequently only observable during physiologic stressors, the most important of which is exercise. Reserve capacity can be measured in a variety of ways that range from overall function (6MWD) to comprehensive assessment of gas exchange and hemodynamics (iCPET). Better understanding of cardiovascular and pulmonary reserve is critical for optimal diagnosis, therapy, and prognosis, and through detailed understanding, the clinician can determine which of these "tools of the trade" are best suited to the individual patient and situation.

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Treating Pulmonary Arterial Hypertension With Exercise: The Role of Rehabilitative Medicine

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Exercise training as treatment has become well established in many cardiorespiratory conditions. This is also increasingly the case in pulmonary arterial hypertension, where several studies have demonstrated improvements in symptoms, exercise capacity and quality of life. There remains, however, much potential for development. Current research is focused on clarifying the mechanism of benefit in pulmonary hypertension and exploring strategies for both optimizing the treatment effect and widening access to this intervention.

HISTORICAL BACKGROUND

Compared with practice in other cardiorespiratory conditions such as chronic obstructive pulmonary disease (COPD) or left heart failure,[1,2] pulmonary hypertension (PH) specialists have arrived relatively recently to the realization of the benefits of rehabilitation for their patients. For many years advice given was to the contrary—that patients with pulmonary arterial hypertension (PAH) should avoid exercise.[3] There are plausible physiological reasons for this cautious position. Increased flow and pressure within the pulmonary arteries might accelerate the disease. The right ventricle is already overworked, dilated and often failing. Patients with PAH can experience exertional presyncope or syncope and even sudden death. Increased exertion would surely only aggravate these problems. However, these views were unsubstantiated and have now largely been superseded by evidence to the contrary.

The benefits of regular exercise training are seen in several domains of human wellbeing and have been demonstrated in many chronic conditions. Not only is there improvement in cardiorespiratory and peripheral muscle function but there are beneficial effects on metabolism, weight management, bone density, mental health, and cognitive function.[4] Greater peak oxygen consumption, the "gold standard" measurement of aerobic exercise capacity, has been repeatedly linked to improved survival in both health and disease.[5]

The first randomized controlled trial to show the benefits of exercise training in PAH was performed in Heidelberg and published in 2006.[6] With only 30 patients divided between the control and treatment arms, this study showed an improvement in functional class, exercise capacity, and quality of life. Over 19 studies investigating rehabilitation in PH have now been published, usually but not always with similar results.[7] This body of work has provided much data on the efficacy and safety of exercise training in PAH and led to a Class IIa recommendation for this as a useful intervention in the 2015 European Society of Cardiology–European Respiratory Society guidelines.[8]

RATIONALE FOR REHABILITATION IN PAH

There is a logical argument for the utility of exercise training in PAH. Using disease-targeted therapy, we can improve pulmonary artery hemodynamics and right heart function.[9] Exercise training is then needed to reverse the concomitant deconditioning and maximize the benefit to be derived from the pharmacotherapy.

Although it is debatable whether exercise training will improve the right ventricle, it can have a definite, beneficial effect on other muscle function. It increases the strength and efficiency of skeletal muscles in PAH.[10] It also improves left ventricular function in both health[11] and disease, even when the primary problem affects the left ventricle.[12] It can also increase respiratory muscle function[13] and may enhance breathing control.[14] From a wider perspective, there can be improvement in perception of symptoms during exercise. Exercise training delivered by a rehabilitation program therefore optimizes the efficiency of training, educates the patients on safe limits, and improves their confidence that exercise is safe, all of which can be significant barriers to exercise. Lastly there are benefits from outside the cardiovascular system such as weight control, improved mental health, and metabolic effects.[4]

OUTCOMES FOR REHABILITATION IN PAH

The benefit of rehabilitation in PH has been tested predominantly in mixed populations of PAH and chronic thromboembolic PH patients, in settings varying from residential to home-based and using a range of outcome measures summarized in Table 1.

Exercise Capacity

There is strong evidence from a Cochrane meta-analysis of randomized controlled trials and from many other

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Table 1. Outcome Measures Used in Pulmonary Hypertension Rehabilitation Studies

Type	Study	Quality of life[a]			Functional ability					Peripheral muscle function	Bio-markers
		SF-36	CAMPHOR	Other questionnaire	6MWD	Peak VO_2	Endurance	WHO Class	Treadmill speed	Muscle strength	NT-proBNP
Inpatient	Mereles et al (2006)[6]	7/10									
	Grünig et al (2011)[15]	7/8									
	Grünig et al (2012)[16]	5/8									
	Grünig et al (2012)[17]	2/8									
	Nagel et al (2012)[18]	2/8									
	Becker-Grünig et al (2013)[19]	1/8									
	Ley et al (2013)[20]										
	Ehlken et al (2014)[21b]	7/8									
	Kabitz et al (2014)[13]										
	Ehlken et al (2016)[22]	1/8									
	Fukui et al (2016)[23]	1/8		PHQ-9							
Outpatient	de Man et al (2009)[10]										
	Martinez-Quintana et al (2010)[24]	SF-12: 0/2									
	Mainguy et al (2010)[25]										
	Fox et al (2011)[26]										
	Chan et al (2013)[27]	6/8	5/6								
	Weinstein et al (2013)[28]			FAS, HAP							
	Raskin et al (2014)[29]			1/3 1/3							
	Zöller et al (2017)[30]	0/2									
	Gerhardt et al 2017 [31]	2/2									
	Talwar et al (2017)[32]										
	Bussotti et al (2017)[33]			HADS, EQ-5							
	González-Saiz et al (2017)[34]	2/8									
Home	Inagaki et al (2014)[35]			SGRQ 1/3							
	Ihle et al (2014)[36]	0/8	1/3								

Legend

	Statistically significant improvement
	No significant improvement
	Statistically significant deterioration

Adapted from Table 7 from Grunig E, Eichstaedt C, Barberà J-A, et al ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. *Eur Respir J*. 2019;53(2):1800332. Reproduced with permission of the © ERS 2019.

SF-36 indicates short-form health survey 36; CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review; 6MWD, 6-minute walking distance; peak VO_2, peak oxygen consumption; WHO, World Health Organisation; NT-proBNP, N-terminal pro B-type natriuretic peptide; PHQ-9, patient health questionnaire 9; FAS, fatigue severity scale; HAP, human activity profile; HADS, hospital anxiety and depression scale; EQ-5, EuroQoL-5 dimensions; SGRQ, St George's respiratory questionnaire.

[a]The number of subscales with significant improvement/number of tested subscales is given. For detailed results of specific subscales of quality of life assessments please see Table 2.

[b]This study refers to the same patients as Grünig et al (2011).[15]

less rigorous studies[7,37–39] that rehabilitation leads to improved exercise capacity in PAH. The most consistent outcome measure used as the measure of exercise capacity is the 6-minute walk test (6MWT). The estimate of the size of the treatment effect was an improvement in 6MWT distance of 60 m.[37] This is a strikingly positive result compared both with the minimum clinically important difference of 33 m[40] and the typical size of treatment effect seen in pharmacological studies of 30 to 40 m.[41] On incremental cardiopulmonary exercise testing, an increase in peak oxygen consumption of 2.41 mL/kg/min was seen.[37] Such an improvement, which represents a 10% to 20% change in this patient group, is impressive as incremental cardiopulmonary exercise testing is generally considered to be an insensitive test for an intervention.[42] Even in a study where no increase of 6MWT distance or peak oxygen consumption were seen, such as de Man 2009,[10] a more sensitive instrument (endurance exercise testing) was still able to show a benefit for the intervention.

Quality of Life

Quality of life (QoL) has principally been measured in the rehabilitation studies using a generic tool (the Short Form 36).[7,37] The analysis reported in the Cochrane review showed an improvement in several domains, namely physical role, vitality, and social function. Physical and mental composite scores were also improved. It would be expected that disease-specific QoL questionnaires would be more sensitive to change. Despite data being available on very few subjects in the studies included in the Cochrane review (n = 18), a significantly improved score was seen in the QoL domain of the Cambridge Pulmonary Hypertension Outcome Review instrument.

Functional Class

Evidence of improvement in functional class is largely available from the earliest randomized controlled trial.[6] Here, of 15 subjects in the intervention group, 6 improved from functional class III to II and one from functional class IV to III.

Peripheral Muscle Function

Patients with PAH are known to have abnormalities of their peripheral muscles including reduced strength, muscle atrophy, impaired contractility, reduced oxidative capacity, and fewer muscle capillaries.[43–45] Rehabilitation has been shown to ameliorate these problems. De Man et al[10] demonstrated that exercise training could increase muscle capillarization, oxidative enzyme activity, quadriceps strength, and quadriceps endurance. Mainguy et al[44] added to this by showing that training caused a reduction in type IIx fiber proportion in the muscles and hence a switch to improved aerobic muscle function.

N-Terminal Pro B-Type Natriuretic Peptide

The N-terminal pro B-type natriuretic peptide (NT-proBNP) assay is a straightforward and widely available assay for detecting impaired cardiac function and hence has been extensively measured in rehabilitation studies in PAH.[7] Reassuringly, exercise training does not appear to lead to an increase in NT-proBNP. On the other hand, unlike other outcome measures such as 6MWT distance and QoL, there does not appear to be an improvement (ie, a reduction) in this biomarker with exercise training. This is at odds with what is seen in several recent pharmacotherapy studies where a reduction in NT-proBNP can be seen in the active intervention arm.[46,47]

Hemodynamics

In a randomized controlled trial (n = 79), Ehlken et al in 2016[48] performed right heart catheterization at rest and exercise pre- and postexercise training in a subset of patients in the trial. At rest (n = 59) they found in the treatment group a fall in mean pulmonary artery pressure of 4 mm Hg and increase in cardiac index of 0.2 L/min/m^2. There was greater change in these values in the adverse direction in the control arm (5 mm Hg and 0.3 L/min/m^2, respectively). The pressures on exercise were unchanged but this represented an improvement as it was in the context of a larger cardiac index in the treatment group (n = 49) where there was an increase of 1.0 L/min/m^2. In support of these findings, there is evidence of reduced pressures seen on transthoracic echocardiogram.[38]

This apparent improvement in function by lowering of cardiac work is in direct contrast with the failure to show a fall in NT-proBNP following exercise training and remains to be explained. It is also unclear why exercise training should improve resting hemodynamics. Such an unsuspected result requires confirmation. A further small, uncontrolled study published only in abstract form so far performed multiple cardiac output measurements during exercise right heart catheterization. They found no change in resting pulmonary artery hemodynamics but did see the same pattern of response as Ehlken et al during exercise.

Survival

There are no reliable data on the impact of exercise training on survival. It is unlikely that this will ever be a useful outcome measure for this intervention because of the size of the study required and the difficulty in controlling for the active intervention which is freely available throughout the patient's lifetime. Some of the other outcome measures that have been used are surrogate markers of survival including, for example, 6MWT distance, functional class, cardiac index, and NT-proBNP.[8] Whilst there is a clear improvement in 6MWT distance, this is counterbalanced by the lack of fall in NT-proBNP.[7] The data on functional class and cardiac index are currently limited. It may be possible in the future to use one of the emerging risk scores[9] linked to survival to provide further information here.

An early animal study did provide some potential concerns regarding survival.[49] A monocrotaline rat model was used to generate 2 subsets of PH, one stable, one progressive and in right ventricular failure. The latter group appeared to show accelerated deterioration when exposed to exercise training.

In summary, exercise training improves symptoms, quality of life, and functional capacity but cannot at this point be claimed to improve survival.

Adverse Effects

The issue of safety in PAH rehabilitation has recently been reviewed in detail

by a European Respiratory Society task force.[7] The amalgamated study data suggest exercise-related safety issues in 4.6% of study participants. However, half of these (2.4%) were due to desaturation, which is a predictable consequence of the disease pathophysiology rather than an adverse effect of exercise training. Of more concern, dizziness, hypotension, or syncope were described in 1.9% of cases and required a change in exercise prescription. Unsustained supraventricular dysrhythmias were seen in 0.4% of participants.

Adverse events not related to exercise were seen in 4.9% of participants, the largest contributor coming from respiratory infection in the group trained in an inpatient setting and leading in some cases to a short interruption to the training program. This finding could simply reflect the background incidence of this common ailment in a more closely scrutinized patient group. However, it is also recognized that exercise can sometimes lead to a suppression of immune function.[50]

Cost Effectiveness

Given that exercise training and PAH therapy can produce similar outcomes in randomized controlled trials, it could be postulated that exercise training could replace PAH therapy in some cases and reduce the cost of treatment. However, this would probably be unacceptable on several fronts. Firstly, there is no direct comparison of exercise training and PAH treatment and unlikely ever to be one for cost and ethical reasons. Secondly, the safety of exercise training without concomitant PAH therapy has not been tested. As discussed earlier, there remains some doubt as to whether exercise training will improve survival in PAH, unlike the case for PAH therapy, where a survival benefit is largely accepted.[51] Consequently, any cost saving attributable to exercise training in PAH patients will be due to reduced escalation of PAH therapy rather than replacement.

One study[21] (n = 106) has performed an economic evaluation of exercise training in PH. As control, this study used an age- and gender-matched patient group not proceeding to rehabilitation. This suggested benefit in the active intervention arm, where there was longer time to clinical worsening, higher quality-adjusted life years, and lower medication costs. However, this was not a randomized controlled trial and the possibility of bias cannot be excluded. In addition, medication for PAH is increasingly available in more economical, generic formulations and any cost effectiveness benefit relying on medication cost may disappear.

Predictors of Response

In the large case series described by Grünig et al,[17] it was possible to identify patterns of poorer response. These were largely non-PAH characteristics including recurrent respiratory tract infections, musculoskeletal problems, and issues with mental health. The other major cause of poor treatment response was in those entering the study with a high 6MWT distance (> 550 m). Whilst this may reflect the reduced sensitivity of this outcome measure at higher walk distances (ceiling effect),[52] it may also indicate an absence of deconditioning in this patient subset, which is likely to be necessary for a positive treatment effect.

A surprising outcome from this case series was that functional class IV patients fared as well as those in functional class II or III. This may be explained by the subjective nature of the functional class descriptor. The baseline 6MWT distance in the functional class IV subgroup was 239 ± 95 m. In other settings these patients would probably have been assessed as in functional class III.

In short, it is likely that there are 3 prerequisites for a response to exercise training:

- stable condition,
- presence of deconditioning, and
- ability to perform exercise.

HOW TO DESIGN A REHABILITATION PROGRAM FOR PATIENTS WITH PAH

Whilst the concept that rehabilitation works in PAH is generally accepted, little of the research data so far have focused on the optimal model of delivery. Features of design of that must be considered in setting up a service are shown in Figure 1.

Most of the data available to guide on the establishment of a service come from the Heidelberg model.[7] The program that they have implemented consists of a 3-week inpatient stay in a rehabilitation hospital followed by 12 weeks of remotely supervised exercise at home. The remaining approaches have largely been outpatient based, both specialized for and restricted to PH patients or enrolled into a generic rehabilitation service. These would typically run over a few months with several short visits to the service each week. There is a small amount of data from patients rehabilitated in a home setting. There is a suggestion from the data in the Cochrane review[37] and elsewhere[10] that outpatient services may be less successful. When the Cochrane review analyzed trials by setting, the Heidelberg-based studies achieved a 6MWT distance of 73 m compared with 34 m in the outpatient studies. There is also an unproven concern that outpatient services, especially those run by generic services, may be less safe. Such statements are largely speculative as there is no head-to-head comparison. On the other hand, outpatient services are undoubtedly cheaper. One problem with outpatient rehabilitation services specific to PH patients that may prove insuperable is the fact that PAH is a rare condition. Hence, achieving a sufficiently large local cohort of patients to make PH-specific outpatient rehabilitation a viable practical option requires a high population density. This will not be true for most patients with PAH who are geographically dispersed. Table 2 contrasts the relative merits of different settings for a PH rehab service.

One striking pattern seen in the Heidelberg model is that all of the benefit is generally achieved by the end of the 3-week stay.[6,17] This raises the possibility of designing a short, intensive, 3-week model that uses a hybrid residential-home format to try to achieve the same results with shorter inpatient stays.

The modalities of exercise training have been generally consistent although different in detail. Aerobic training has been delivered by walking (outdoors or treadmill) or cycle ergometry.[7] Some features used may enhance the effectiveness of the training. In the Heidelberg

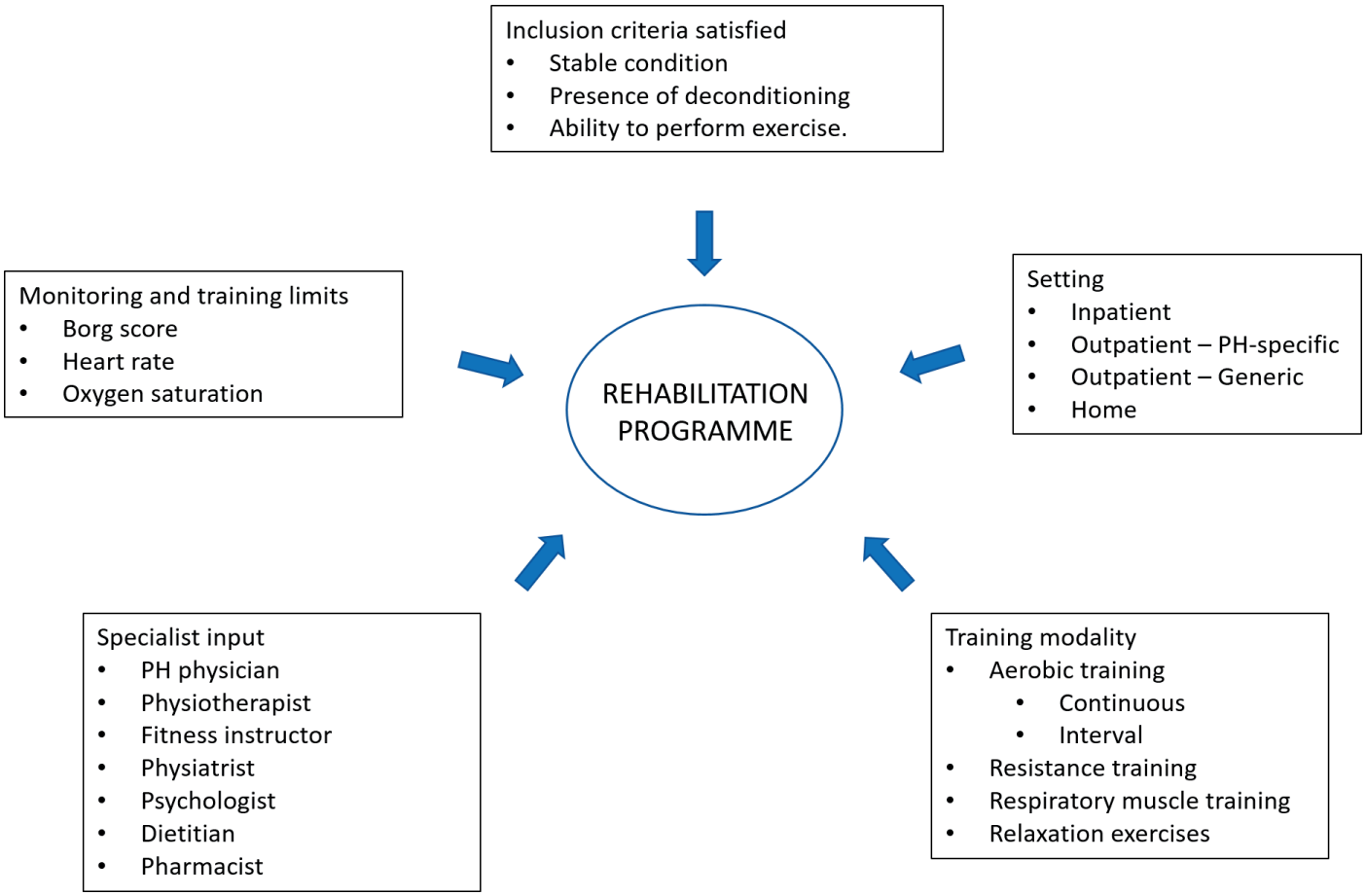

Figure 1: Design features to be considered in setting up a pulmonary hypertension rehabilitation service.

model, exercise training workloads start low and are continually reassessed and increased during the program. This gives patients an impression of progress and reinforces compliance. Several of the rehabilitation programs used interval training rather than continuous training models, an approach that tends to optimize the efficiency of the training process.[53] Attention was paid to the maintenance of minimum oxygen saturations and the use of oxygen supplementation where required.[7] This is an approach recognized to increase exercise capacity and thereby improve the intensity of training and hence the training effect.[54]

Low-level resistance training was also widely used[7]. However, the use of relaxation therapy and respiratory muscle training were less widespread.[7] Respiratory muscle weakness is an unexpected feature of PAH which has been convincingly demonstrated.[55] A small uncontrolled study of 7 patients[13] received inspiratory muscle training as a part of their exercise training program. Inspiratory muscle strength increased when tested in a nonvolitional manner. Inspiratory muscle training has also been used as the sole intervention in 2 studies.[56,57] Respiratory muscle strength assessed by mouth pressure was increased but improvements were also seen in exercise capacity and quality of life. A similar effect in a larger patient group has been demonstrated in patients with left heart disease.[58,59]

Monitoring of exercise training is described in most studies and typically employed a combination of Borg score, heart rate, and oxygen saturation. These are useful both for monitoring safety and assessing intensity of training. The precise limits used in the studies are summarised in the recent European Respiratory Society task force statement.[7] Lastly, rehabilitation services generally utilize the skills of a wide range of specialists. In the PH rehabilitation studies, there has been involvement of PH physicians, physiotherapists, physiatrists, psychologists, fitness instructors, dietitians, and pharmacists.[7]

Table 2. Relative Merits of Different Settings for a Pulmonary Hypertension (PH) Rehabilitation Service

	Inpatient then home	Outpatient: PH specific	Outpatient: generic	Home
Efficacy	+++	++	+	+
Cost	High	Moderate	Moderate	Low
Safety and monitoring	++++	+++	++	+
Accessibility	+	–	++	+++

THE FUTURE OF REHABILITATION IN PAH

Attitudes to activity and exercise for PAH patients have been completely reversed over the last 15 years. PH physicians are convinced that physical rehabilitation helps their patients. The focus now is on the optimal model for delivery of the intervention, which inevitably is a compromise between efficacy, cost, and accessibility.

The most effective approach may well vary country to country or even between PH clinics and there are a number of variables yet to be fully explored. Examples include the setting of the program. Would short-burst inpatient training with several stays of 1 to 2 days spread over 3 weeks be as effective as a 3-week continuous inpatient stay? Alternatively, would local, generic outpatient rehabilitation delivered alongside other cardiopulmonary patients be as effective as PH-specific programs? The advantage of both these approaches would be an improvement in cost and accessibility. Another variable is the form of exercise training and standardization of the exercise prescription together with use of adjuncts such as oxygen supplementation. Should respiratory muscle training be universally adopted bearing in mind that its role in rehabilitation in COPD has been much more intensively investigated and is currently out of favour?[60] Are there mechanisms of improving peripheral muscle training without overstressing the cardiopulmonary system such as the concept of single-leg exercise that has been used in COPD and heart failure?[61]

Some questions have yet to receive any attention, such as the timing of the rehabilitation in the disease process—at diagnosis or after pharmacotherapy has been optimized? Also what is the potential role for widely available motivational aids such as internet-based videos and "fitness watches," which represent an as yet untapped resource?

In consequence, there is a clear role for rehabilitation in PAH and this area of therapy is currently in an early phase of development for our patients. We should expect many changes in this area in the coming years.

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The Role of Exercise in Clinical Practice and Clinical Trials

On May 20, 2019, Guest Editor Ronald Oudiz, MD, Director of the Pulmonary Hypertension Program at Harbor-UCLA Medical Center in Los Angeles, California, led a discussion with Aaron Waxman, MD, PhD, Director of the Center for Pulmonary Heart Disease at Brigham and Women's Hospital and Harvard Medical School in Boston, Massachusetts, and Robert Naeije, MD, Professor Emeritus at the Free University of Brussels, Belgium.

Dr Oudiz: Today, we're going to talk about many concepts in exercise as they relate to pulmonary hypertension, specifically, diagnosis, prognosis, and treatment. Let me start off by saying thank you to Robert and Aaron for joining us in this discussion today.

The first topic I'd like to touch on is, how can exercise help us in our diagnosis of pulmonary hypertension in terms of helping us understand the nature of the limitation of the patient with pulmonary hypertension, helping us understand or categorize pulmonary hypertension? Then we will go from there. I'll start with Aaron. How would you approach the answer to that rather broad and generic question?

Dr Waxman: I think from a very broad worldview, I look at exercise as an additional screening tool, specifically when we talk about exercise with the addition of gas exchange and some sort of protocolized approach. There are some physiologic parameters that we can see with exercise testing that might tell us there's a physiologic defect, but it's not going to give us a diagnosis per se.

Dr Oudiz: Robert, how is exercise important in the broad scope of pulmonary hypertension? Why is it important?

Dr Naeije: If we are still discussing the diagnosis or use of [cardiopulmonary exercise tests (CPETs)] for diagnosis, I would say that I agree with Aaron that exercise testing is for functional diagnosis, not for clinical diagnosis. When a patient is referred to the [pulmonary hypertension (PH)] center, we perform a CPET as part of the initial workup to assess whether or not the exercising profile fits with the diagnosis of pulmonary hypertension.

Dr Oudiz: Would you all agree that an evaluation of a PH patient that includes resting echocardiography, as well as resting hemodynamics, is a rather incomplete evaluation of this patient, without the knowledge of what happens to the patient when they exercise?

Dr Waxman: I would certainly agree with that. I would also echo what Robert had said earlier. We do exercise as part of our complete pulmonary hypertension evaluation from the approach of unexplained dyspnea. It informs us of the contributors to shortness of breath and exercise limitation. It also provides us a physiologic baseline to compare back to when we start treatment. To me, that's the real power of the exercise test at the time of diagnosis, to track the impact of treatment.

Dr Naeije: I fully agree. We always did and still do an initial CPET whenever a patient gets into a workup process for the diagnosis of hypertension. It's really essential because it's not only about functional profile; it's the understanding of the contribution of the disease to exercise limitation in the follow up, for early detection of the duration, and understanding of the effects of therapeutic interventions.

In Brussels, we really use CPET in the initial diagnostic process, but then also in follow up and on a regular basis for better understanding of the patient's symptoms and the effects of drugs.

Dr Oudiz: Robert, you talked a little bit about categorization of PH I think. Would you agree that, in patients whom we see who have maybe a little bit of interstitial lung disease, maybe a scleroderma patient, and maybe they're older and you suspect that they have diastolic dysfunction, that sometimes we aren't absolutely sure, even after we've done the complete workup according to the classic diagnostic algorithm, if the predominant physiology indeed is a pulmonary vascular limit to exercise? And therefore, the exercise test, particularly with gas exchange, may be helpful in helping to confirm or refute the diagnosis of one kind of pulmonary hypertension.

Dr Naeije: I certainly agree. In the process, as you allude it to, the trick is to assess the contribution of chronic lung disease, essentially. Of course, you also have the lung function test to help you in that, and I think blood gases are really important. In the end, in using the results in our staff meeting discussions, I think we've focused very much on the ventilatory responses.

A patient who is hypercapnic or who becomes hypercapnic during exercise does not have pulmonary arterial hypertension, or has it with symptoms overwhelmed by the ventilator limitation of lung disease. The interpretation of CPET requires also lung function tests, and thus lung mechanics and blood gases to assess gas exchange. That's how it mainly goes because patients with PH or heart failure, when they're symptomatic enough to go to the hospital, they're hyperventilating, and they have an increased ventilation for this level of CO_2 output, and they tend to be hypocapnic. A patient who is not hypercapnic and not hyperventilating is probably not PH, in our experience.

Dr Waxman: I would add to that. One thing we've already learned from the [Pulmonary Vascular Disease Phenomics (PVDOMICS)] Network is that there is almost no such thing as a single entity

of PH, that very often in the real world, there's overlap of multiple [World Symposium on Pulmonary Hypertension (WSPH)] groups in each patient. To be able to differentiate some of those contributors to dyspnea when you're starting to treat a patient, it can help guide you and inform the patient why certain medication may require adjustment, may not fully resolve the patient's dyspnea, or other therapies may be indicated.

Dr Oudiz: You're both referring specifically to gas exchange measurements. Can you talk a little bit about how exercise has been used in PH clinical trials in the last 20 years?

Dr Waxman: I think there's good and bad that's happened in clinical trials. Obviously, the 6-minute walk test has been the hallmark exercise test. I think, as we've moved into the phase of most patients entering clinical trials on multiple background therapies, the 6-minute walk test becomes less and less helpful. Unfortunately, with CPET, we had previous clinical trial protocol designs where there were no specified exercise protocols and no central reading core; every study site was doing it their own way. The readout was done differently in each center.

I think, if we could redesign trials to include CPET utilizing a clear exercise protocol that was performed the same way at every site, and all the data [were] analyzed at a single central core, we would probably get more out of those trials. I think it would be much more informative, especially with multiple background therapies.

Dr Naeije: Yes, surely true. In fact, there were 2 trials in which peak $\dot{V}O_2$ was the primary endpoint: the drugs tested were sitaxsentan and beraprost. Both failed on the primary endpoint, while there was a significant improvement (with sitaxsentan) or trend to improvement (with beraprost) in the 6-minute walk distance, suggesting efficacy.

As Aaron alluded to, there's really a problem of quality control of CPET in many centers, even some reputation and tradition, because access testing is not as easy as it seems, even when it's automated in new digital devices, more recent devices. Moreover, with tested monotherapies, the effect size on peak $\dot{V}O_2$ or any other CPET variable is usually very small. The 6-minute walk test is easier to standardize and more sensitive to therapeutic interventions in severe PH. This is why many [pulmonary arterial hypertension (PAH)] drugs were made available after positive trials with 6-minute walk as the primary endpoint.

If your peak $\dot{V}O_2$ changes from say, 11 to 12.5 or to 13, I think, on average, you would have 1.5 to 2 mL/kg/min. You have an error on the measurements that's about the same range. Of course, you cannot expect trials to become positive. I think that, currently, many centers are learning to do it better, and we have more efficacious multidrug therapies with more impressive changes in hemodynamics and 6-minute walk. It is now very likely that, should we do it again, peak $\dot{V}O_2$ is a primary endpoint with a triple initial combination therapy, such a trial would be positive.

Dr Oudiz: Robert, it's been my impression that, in the [European Union (EU)], there are PH experts that not only believe in, but actually use gas exchange measurements, more so than in the United States. Aaron, maybe you see that, or maybe you disagree?

Dr Naeije: No, I'm not sure about that. I think it's a general phenomenon. Further, on the subject of trials, it is intriguing that, in considering CPET as primary endpoint rather than the 6-minute walk, it was only about peak $\dot{V}O_2$, while several studies have shown that, like in advanced left-sided heart failure, the ventilatory equipment for CO_2 ($\dot{V}E/\dot{V}CO_2$) is more sensitive to clinical state and a more potent predictor of outcome. Maybe in single drug trials in PAH, $\dot{V}E/\dot{V}CO_2$ would have been more sensitive to the tested intervention. This would be something to revisit in databases. Again, CPET is not only peak $\dot{V}O_2$, there are lots of other measurements. Maybe also we should have considered a combination or composite CPET measurement score if we had more seriously discussed the use of CPET as primary endpoint in these studies.

Dr Oudiz: You know, the regulatory agencies are one of the determinants of what an endpoint will be in a PH clinical trial, particularly in a trial that is used for registration of a new drug. I'm somewhat familiar with [Food and Drug Administration (FDA)] guidance that $\dot{V}E/\dot{V}CO_2$ today doesn't seem to be an acceptable endpoint; however, peak $\dot{V}O_2$ would be. I agree with you that $\dot{V}E/\dot{V}CO_2$ may be the better measurement, and certainly, the more relevant measurement clinically. Aaron, do you think that's true?

Dr Waxman: I think I would agree 100%. That would open the door also not just at maximal testing, but also submaximal testing, which might be an easier approach to a clinical trial. We do that now as part of our clinical practice. Using a simple 5-minute submaximal step exercise test, we track several simple objective readouts, such as the $\dot{V}E/\dot{V}CO_2$ slope, as well as measurements of end tidal CO_2, all as indirect measures of blood flow. I think that has real potential, both in daily management of these patients and their responses to treatment, as well as a potential outcome measure in a clinical trial.

Dr Oudiz: Great. Well, let's do a little bit of a shift and talk about exercise hemodynamics because the theme of this journal issue is exercise, not only gas exchange, but also what exercise can do to either unmask or characterize the nature of one's pulmonary hypertension. Is it done fairly regularly, and if so, is there a standard protocol, and where would we find that protocol?

Dr Waxman: Invasive CPET is done regularly in a small number of centers. Our center at the Brigham and Women's Hospital does a lot. I think we do close to 400 a year. We have refined and standardized our protocol over many years, but that's not to say that other centers don't do it differently. One big difference between centers is whether it's done in the supine, upright, or semirecumbent position. We have always focused on doing upright because that's how patients live and function day to day. We felt that was most reflective of true normal, or

what the patient experiences when they are dyspneic on a regular basis.

Dr Oudiz: Is there a role for those centers that may not have expertise in gas exchange to do exercise hemodynamics alone without the gas exchange?

Dr Naeije: Combining exercise hemodynamics and CPET is ideal but really challenging, but exercise hemodynamics and CPET can be done separately. Exercise hemodynamics can be noninvasive. What matters most is stressing the cardiovascular system if one is aiming at the detection of latent disease or complex differential diagnosis.

Dr Waxman: I think, if you do it without gas exchange so that you don't have a $\dot{V}O_2$ measurement, then you need to be at least aware of how to determine a cardiac output properly. Technically, if you're going to do it right, you need to change the exercise protocol so that you can do an accurate thermal dilution, but thermal dilution is really hard to do in that setting. You can't use an assumed fit or an estimated $\dot{V}O_2$ in that setting. That's the one major drawback.

Dr Naeije: In my center, we prefer to do CPETs and exercise hemodynamics separately. Of course, combining CPET and exercise hemodynamics, as done in some centers, is still worthwhile, too, for research purposes. The approach has allowed for a lot of progress in the understanding of exercise-induced PH, differential diagnosis of unexplained dyspnea, and effects of rehabilitation programs.

We know the limit of normal of exercise hemodynamics even better than those of various CPET measurements. All these measurements have to be integrated in the context, of course. The ideal is to do it all together, like in Aaron's center, but practically, in many centers, we all have to dissociate these examinations, and sometimes we satisfy for a while with a noninvasive approach.

Dr Oudiz: Great. Aaron, you said you were doing 400 per year. How is it done?

Dr Waxman: Our approach is, first, in the [catheter] lab, to place a right heart catheter through the internal jugular vein using local anesthesia. We generally use a Paceport Swan so that we can record pressures, obtain wave forms simultaneously from the right atrium, right ventricle, and pulmonary artery. We wedge the catheter every minute during the test to get a pulmonary arterial wedge pressure. We also place a radial arterial line so that we can draw an arterial sample as well as the venous sample every minute.

We are measuring gas exchange continuously, and the patient will perform a full symptom limited incremental load standard cardiopulmonary exercise test. We first get measurements at rest, then the patient will start with 2 minutes of unloaded cycling, and then they go into a ramp protocol. That workload ramp is based on what the patient tells us prior to the test, same as we would do with a standard noninvasive CPET. We have the patient exercise to peak exercise, that point of exhaustion, we take away the workload, and then we'll do 2 minutes of recovery phase.

The other important benefit of invasive CPET, especially when you have patients who have respiratory issues and might hyperventilate during the test, is that we have a number of different ways of being able to measure the peak exercise points, beyond just the [respiratory exchange ratio (RER)] and heart rate. We can look at the venous pO_2 (<29 mm Hg), and track the $M\dot{V}O_2$ (<27%) and cardiac output (>80% of max predicted) as well as measuring arterial lactates and a host of other dynamic Fick principle data.

Patients tolerate it really well. We have patients who even volunteer for a second time as part of studies. Importantly, the first test is always a clinically indicated test to evaluate unexplained dyspnea as well as characterize pulmonary vascular disease.

Dr Oudiz: It's quite impressive in what you do, and you make it sound maybe not simple, but not impossible, yet I think, for many of us, as Robert had pointed out, there are certain barriers in the sophistication of one's lab, let alone an understanding of the physiology and how to marry the 2 technologies. Congratulations are in order.

Do you think there is potential for either you or others to teach the rest of us, or at least teach those qualified to learn, and going forward, will there be more centers worldwide that are doing this?

Dr Waxman: Absolutely. In fact, I can tell you that there are centers that will come and visit with us, spend a day or two just seeing how we do it, and they're starting to develop their own programs. That's what's happening at the University of Pittsburgh. Cornell is setting up a program. Obviously, the University of Arizona and the Mayo Clinic in Rochester, Minnesota, have been doing it for a while.

In fact, as part of our program to evaluate the cause of unexplained dyspnea, we are having to set up 2 satellite centers in our area because we're booked out so far. These centers will be in community hospitals. It can be done. I think the biggest hurdle is just the concept itself; most people think of a Swan only in critically ill patients. The approach is very safe, and it can be done in a fairly routine manner.

Dr Oudiz: That's great, Aaron. Let's touch a little bit on exercise as it relates to risk assessment. Robert, I know you have a strong opinion on this.

Dr Naeije: CPET variables have a tendency to disappear in recently adjusted European [European Respiratory Society/European Society of Cardiology (ERS/ESC)] guidelines for risk assessment scoring systems for PAH patients. The US-derived [Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL)] score, which is the most rigorously validated risk assessment score in PAH, never included CPET variables. The problem with currently available risk assessment scores in PAH is that they were fed with data available in most PH centers. Only a minority of PH centers rely on CPET. The same can be said, unfortunately, about imaging, by echocardiography or magnetic resonance imaging. So the absence of CPET or imaging variables in risk assessment scores does not argue for the futility of these measurements.

We have to understand this because, with all the current risk assessment scores, we can predict very poor outcome, and we can predict excellent outcome. The majority of patients will stay in some sort of a gray zone. I think that wasn't enough encouragement currently to revisit CPET, but also echo imaging, which is available, and collect in a multicenter way a maximum of this data and see if we can improve the prognostication in PH based on scores.

Dr Oudiz: Yes, Robert, I agree that the guidelines fall short of exploiting the great virtues of CPET in prognosis, and this is based on a lack of data. I suppose the main question is, how are we going to get data? How can we get more systematic, unbiased, maybe multicenter data going forward?

Dr Naeije: More multicenter collaborations and more centers devoting time and energy and resources to CPET are crucially needed. We need to convince all these people to work together and to build up new databases, largescale and main centric to improve our capability to assess risk. That's very important in adjusting therapies.

I was alluding, initially, to the apparent great success of initial triple combination of drugs targeting different pathways in PH when patients initially get their diagnosis and really encouraging data coming. It's very, very expensive and difficult to do. It would be better if we had improved tools to assess risk and use the full capability of all the CPET variables to adjust and probably be able to prescribe in a more rational way double combinations or maybe single drug therapies that will be equally efficient.

Dr Oudiz: Sure. Aaron, are you aware of any efforts, either on your own or multicenter, US or worldwide efforts to acquire this data for risk assessment?

Dr Waxman: As part of the PVDOMICS Network, which includes 6 clinical centers, we are doing CPET on the majority of patients. The goal is to do everyone, but some patients aren't able. We'll have a very robust dataset of both invasive and noninvasive CPET in patients, and there is a longitudinal component to the study. Yes, we should have that data. I would expect that we probably already have that data if we were to combine some centers now from a noninvasive CPET standpoint. That approach would be retrospective, but the data from PVDOMICS will be prospective data.

Dr Oudiz: Hopefully, that will be coming soon. Moving onto our final topic of exercise as an intervention for patients with pulmonary hypertension or, if you will, rehabilitative exercise, what is your opinion of exercise from the standpoint of is it safe? Is it effective? Are you using it, Aaron?

Dr Waxman: It is absolutely safe. Because of our experience with maximal exercise testing and invasive testing, we've found it to be very safe. Part of our treatment program in our pulmonary vascular program is exercise. Our exercise physiologists meet with and prescribe a graded exercise program for every patient who goes on treatment. Compliance may not be 100%, but patients definitely do improve just with exercise. The literature is starting to bear that out as well.

Dr Naeije: Back to risk assessment, there is one study which demonstrated added value of CPET. It was done by our colleague Badagliacca and his coworkers at the University of Rome. However, it was on a relatively small cohort of 100 patients with long-term follow-up. It was a step in the right direction, but we need multicentric efforts.

Back to the rehab, I was involved in some of the pioneering studies done by Grunig and his coworkers. Rehabilitation is beneficial in PAH. It may improve exercise capacity, even in patients under optimal multidrug treatments.

The problem I find with rehab programs in PH is that they really work best if done as inpatients in dedicated centers for several weeks. Attending twice or thrice a week a rehab center, on an ambulatory basis, may be too challenging for PAH patients already exhausted by using public transport, climbing stairs, and walking long corridors. Otherwise, exercise training in PAH is safe, except for obviously too ill patients in right heart failure.

Dr Oudiz: That's one of the questions I think that many of us have in terms of the durability of the intervention. If the exercise is maintained to some degree for the patients on their own or in a continued monitored setting, I think the benefits would be clearly sustained. However, at least in the US, it's not feasible to have paid programs support ongoing supervised exercise, and therefore, the prescription is often taken home, and the compliance over the long term has yet to be determined.

Dr Naeije: In recent years, we have seen the development of a lot of monitoring devices, not only invasive PA pressure which remains investigational, but also simple movement monitoring by actimetry, which is by the way already accessible in iPhones. If centers can use these devices to maintain dialogue with the PH patients and monitor the activity and preferably also progress, I think we might improve the situation.

Also, it's a matter of training. When the patients have a good start for a couple of weeks in the dedicated rehab center, and then with a dedicated team staying in contact with the patient so that they continue prescribed exercise daily exercising at home, then the results are very good. There is now a network of such centers in Central Europe; the results are excellent.

Dr Waxman: I would add to this by saying that we're actually working on a wearable device to pair with a prescribed home exercise program so that we can track a patient's activity and be able to assess them on a weekly basis with a very short predefined home exercise test that includes heart rate recovery and a measure of effort during that exercise. I think that will also provide motivation for patients to keep it up.

Dr Oudiz: The advent of better technology and patient-specific targeted therapy is happening even in the home now, Aaron. It sounds wonderful.

Dr Waxman: I think it's really where we're headed. I think it will make the patients much happier.

Dr Naeije: I fully agree it's the way to go, but the loads on the PH team or the rehab team which is staying in the reference center, the workloads on these teams will remain important because it is time consuming and it takes dedication to monitor [these] data on a daily basis or even summaries and to maintain contact with these patients. The cost of rehab programs and home monitoring devices will be an important issue.

We'll see if the insurances can cover that and if it's simply financially feasible to do that because it cannot be developed simply based on the goodwill of interested teams. We need some structure and, of course, evaluation. I agree with Ron that we don't know yet how well it works. It's really likely that it will work just fine, but we need more data, and we need to structure these kind of systems to have it directly funded. Otherwise, it's going to die off, I'm afraid.

Dr Oudiz: Gentlemen, thank you so much. It has been a really a nice treat to have your expertise and discuss an important and timely issue such as exercise in PH. I hope that there are more things to come in the world of exercise PH.

ASK THE EXPERT

What Is the Exercise "Prescription" That You Provide to Your Patients?

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There is no single exercise prescription for all pulmonary arterial hypertension (PAH) patients, both because of the uniqueness of each individual patient's disease state and because the experts do not understand the full multifaceted impact of PAH. The challenge does not end with the development of an effective exercise program because getting anyone to start and maintain an exercise program is difficult, much less PAH patients who can struggle with simple day-to-day activities. However, I believe PAH patients, like other patients, benefit from an appropriately tailored exercise regimen as part of a holistic approach to improving physical and mental health.

As far back as the ancient world, Hippocrates and Galen understood that exercise is a necessary part of overall health. Hippocrates wrote, "Eating alone will not keep a man well; he must also take exercise. For food and exercise. . . work together to produce health."[1] Unfortunately, with our increased understanding of how to manipulate the body with medications and treatments, some of the original focus on holistic well-being has faded, and Western medicine has become more focused on "sick care" versus "health care." I believe integrating exercise into a treatment plan helps put the focus back on wellbeing.

While our understanding regarding PAH has improved dramatically, including the development of many new therapeutic options, the true impact of PAH has not been adequately quantified nor optimally addressed. The general conclusion among surveys is that the clinical definition of the severity of disease appropriately includes symptomatology, exercise capacity, biomarkers, invasive and noninvasive haemodynamic measurements, and survival.[2] However, even these parameters do not capture the complexity and the interconnectedness of physical, emotional, and psychosocial issues which affect patients and their caregivers.[2] Accordingly, practitioners are faced with the challenge of creating an exercise plan without clear established clinical guidance.

That said, recently, more attention has been paid to health-related quality of life (HRQoL) in PAH patients and how a multidimensional approach to patient care and treatment may improve prognosis. This approach takes into account the individual patient's perspective regarding their disease and the impact it has on their life. A patient-centered collaborative care approach to provide optimal care must be multifaceted in order to address the physical, psychological, social, and informational needs of patients and caregivers, alongside their clinical needs.[2] I believe an important aspect of this multidimensional approach includes exercise.

Unfortunately, exercise, even for healthy individuals, can be daunting and conjures up thoughts of dread and procrastination: running the mile in physical education class as a child, images of CrossFit athletes flipping truck tires, or unfulfilled New Year's resolutions. Now imagine prescribing exercise to patients with PAH who have difficulty doing their daily activities. As such, one of the first responsibilities of practitioners is to destigmatize the word exercise and strip away its traditional connotations. Exercise is simply any bodily activity that enhances or maintains physical fitness and overall health.

Adding to the difficulties addressed above, many PAH patients receive misinformation regarding their own health, ability, and prognosis. I often hear: "I was told not to exert myself because it could cause my heart to fail." Previously, PAH patients had been advised against strenuous exercise for concern over possible risk of sudden cardiac death, increased pulmonary remodeling related to the sheer stress of activity, and worsening of right heart failure.[3]

It is true that any exercise "prescription" should begin with a discussion that includes advising against excessive physical activity that could lead to exacerbation of symptoms and that, prior to initiating a supervised exercise program, the patient should be treated with the optimal pharmacological therapy and be in a stable clinical condition, but once those safeguards are in place, it is recommended that patients should be advised to remain active within symptom limits.[4] In fact, several randomized controlled trials (RCTs) have demonstrated the improvement in functional capacity as well as QoL in patients with PAH. Recent RCT publications indicate decreased fatigue severity and improved 6-minute walk distance, cardiorespiratory function, and patient-reported QoL when compared to untrained controls.[3,5,6] Additionally, the most recent

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American College of Clinical Pharmacy PH guidelines suggest that patients with PAH should be involved in some type of supervised exercise as part of the integrated care for their disease as an ungraded consensus-based statement.[7]

Unfortunately, the evidence currently available regarding rehabilitation and exercise among patients living with PAH lacks any specific exercise program. The European Society of Cardiology/European Respiratory Society 2015 guidelines note that their recommendation is limited due to gaps in the knowledge of an optimal exercise program and the intensity or duration of exercise.[8] However, throughout the guidelines, it is clear that exercise should be part of a PAH patient's care plan with appropriate guidance on how to manage individual physical limitations and symptoms.

Due to the lack of data in the area of rehabilitation, the amount of supervision, mechanisms for the improvement of symptoms, exercise and functional capacity, and possible effects on prognosis are unclear.[8] However, in many ways, this lack of clarity allows for each treating expert and center, in collaboration with the individual patient, to devise an appropriate care plan for each patient. Given the uniqueness of each patient, this flexibility may actually improve the chance of successfully tailoring an exercise program.

In summary, the most recent guidelines recommend exercise/rehabilitation for PAH patients. Accordingly, when prescribing an exercise program, I address risks, seek to ensure a stable clinical condition and environment, and educate my patients on the positive results of exercise in all people and specifically in PAH patients. We discuss the multidimensional approach that we will take together to focus on all aspects of the disease and wellbeing. I encourage and enroll my patients in rehabilitation after diagnosis and initiation of appropriate therapies and control of their disease for a further tiered approach to their overall treatment. In close collaboration with our rehabilitation program, we devise a low workload exercise protocol and focus on further education and understanding of their disease and abilities. I have found that, not only does this improve my PAH patients' exercise tolerance, but they achieve an improved sense of physical and mental wellbeing.

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A Case of Pulmonary Hypertension Associated With High Cardiac Output State from Arteriovenous Fistula–Or Is It?

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PRESENTATION

A 74-year-old male initially presented to the cardiology service in 2011 for evaluation of possible ischemic heart disease. The patient reported shortness of breath without chest discomfort after walking 100 to 200 yards (91.4 to 182.8 meters) (NYHA FC III). A persantine nuclear examination prior to initiation of dialysis for end-stage renal disease (ESRD) and prior to dyspnea becoming severe was reported by the patient as unremarkable. Dyspnea had been troublesome the last 3 to 3.5 years, was relatively stable, but was limiting to activities of daily living and exertion.

Past medical history was pertinent for hypertension, right kidney neoplasm, insulin dependent diabetes mellitus type II, hypothyroidism, paralysis of right hemidiaphragm, chronic anemia, and ESRD due to diabetic nephropathy (hemodialysis via left upper extremity arteriovenous fistula [AVF]). Social history: Tobacco, 36 to 54 pack years; stopped 33 years ago. He denied alcohol consumption or recreational drug use.

Physical examination: Appearance: no acute distress. Blood pressure: 180/70 mm Hg. Well-developed AVF left arm. Cardiac: without murmurs, gallops, or rubs. Lungs: clear. Abdomen: nontender. Extremities: without cyanosis, clubbing, or edema.

EKG: Axis 90 degrees, normal sinus rhythm and first-degree heart block.

Echocardiogram (August 2011): Normal left ventricle size with mild to moderate left ventricle hypertrophy, left ventricular ejection fraction (LVEF) 65%, no wall motion abnormalities, grade 2 diastolic dysfunction, mildly dilated left atrium, right ventricle (RV) upper limit normal size with normal systolic function, trivial tricuspid regurgitation with pulmonary artery systolic pressure (PASP) 47 mm Hg, mildly dilated right atrium, unchanged from August 2010.

Chest fluoroscopy: Paralysis of the right-hemidiaphragm.

Pulmonary function testing: FVC 2.38 L (54% predicted), FEV1 1.82 L (52% predicted), FEV1/FVC 76, FEF25-75 1.42 L/sec (41% predicted), TLC 5.40 L (79% predicted), DLCO corrected for hemoglobin 23.08 (84% predicted).

Arterial blood gas (resting room air): pH 7.38, PaO2 61 mm Hg, PaCO2 45 mm Hg and calculated bicarbonate 27 mmol/L.

At that point, it was felt that symptoms were likely caused by diastolic dysfunction from severe hypertensive heart disease. Symptoms were not felt to be ischemic, although there were multiple risk factors for coronary artery disease.

Multiple echocardiographic studies showed gradual progression of PASP from 40 mm Hg (2006, pre-fistula) to 90 mm Hg (November 2013); the latter echocardiogram also demonstrated severe RV dilation, moderate right atrium (RA) enlargement, ventricular interdependence with normal LVEF and grade 1-2 diastolic dysfunction (Figures 1–4).

Because of the previous echocardiogram (November 2013) and worsening symptoms, right heart catheterization (RHC; February 2014) was performed after hemodialysis: RA 15/13(10), RV 90/0(16), pulmonary arterial pressure (PAP) 96/31(58), pulmonary capillary wedge pressure (PCWP) 10/13(10), cardiac output/cardiac index (CO/CI) (TD) 7.0/3.6, CO/CI (Fick) 4.9/2.5, pulmonary vascular resistance (PVR) 7.4 WU, TPG 48.

Further evaluation included a low probability V/Q scan, normal LFTs and TSH. Sleep study was refused by patient.

To determine if the symptoms and the pulmonary hypertension could be secondary to AVF rather than anemia alone, RHC was repeated pre- and post-occlusion of the AVF (Table 1).

There was a 22.5% drop in cardiac output after occlusion of AVF for 5 minutes. To ameliorate high cardiac

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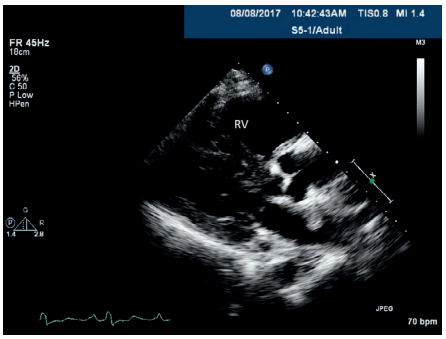

Figure 1: Parasternal long axis view showing early right ventricular changes (also see supplemental clip 1).

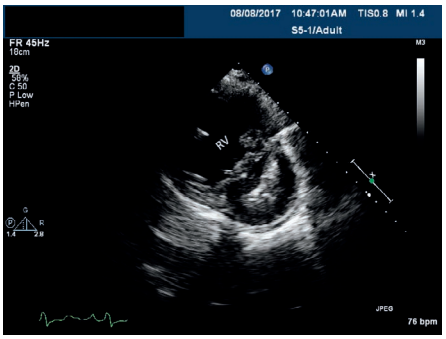

Figure 2: Parasternal short axis view showing severe right ventricular dilatation, small left ventricle, and D sign with flattening of interventricular septum.

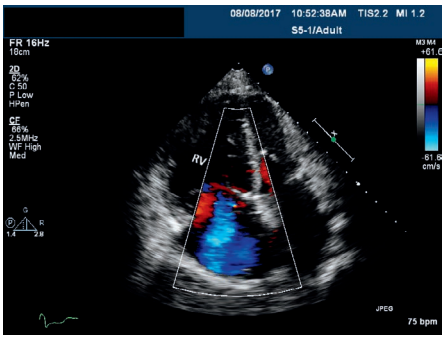

Figure 3: Apical 4-chamber view showing severe tricuspid regurgitation and severe dilated right atrium and right ventricle (see also supplemental clip 2).

output from the AVF, the fistula was surgically ligated and a tunneled dialysis catheter placed. Repeat RHC (October 2014) again demonstrated marked pulmonary hypertension despite closure of AVF, suggesting progression of intrinsic pulmonary vascular disease. Therapy with a PDE-5 inhibitor (sildenafil) and, 1 month later, an ERA (macitentan) was initiated. The patient reported no symptomatic improvement with sildenafil and thought he was a little worse when macitentan was added. Overall, there

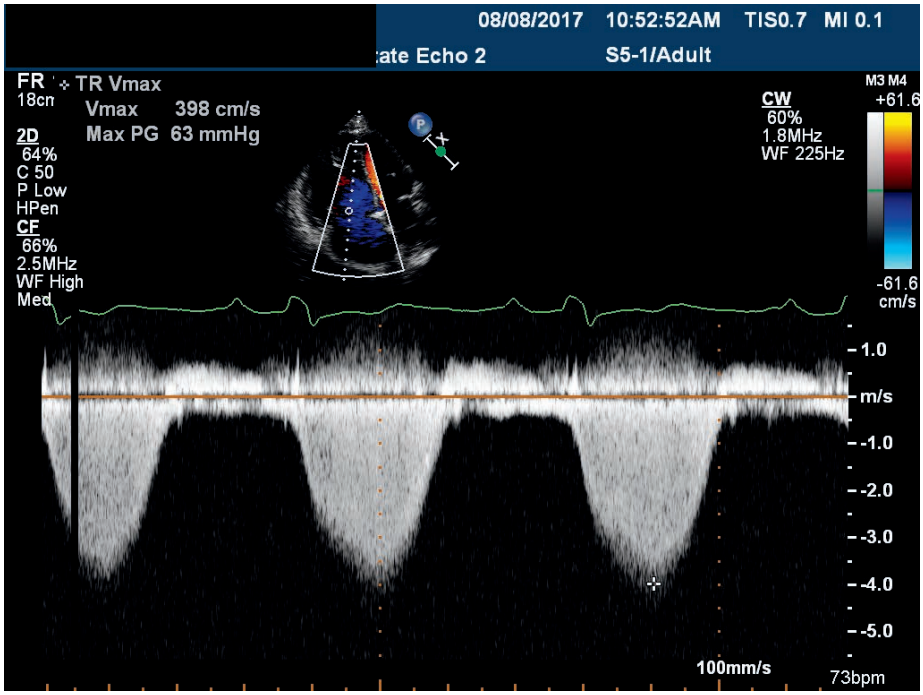

Figure 4: Continuous wave spectral Doppler demonstrating severe pulmonary hypertension.

was no clear benefit with these therapies; however, there were no side effects, especially peripheral edema. Sildenafil was discontinued because of low blood pressure, and macitentan was discontinued by the patient's nephrologist.

Because of lack of change in symptoms and a 6-minute walk distance of 183 m, RHC was repeated and showed mPAP of 50 mm Hg, pulmonary capillary wedge pressure of 13 mm Hg, and cardiac output of 8.36 L/min. Because of the high cardiac output, the presumedly closed AVF was re-evaluated by fistulogram and demonstrated collateral blood flow from the brachial artery to the cephalic vein. The patient then underwent complete resection of the AVF. RHC 6 months later showed PAP 88/27 (53), PCWP 7, and CO/CI (TD) 6.54/3.41.

Additional Data

NT-proBNP 18 710 pg/mL (09/14), 4379 pg/mL (06/15), 29 469 pg/mL (11/15)

Hepatitis B surface AB 451 (high) (07/06), negative hepatitis A, hepatitis C and other hepatitis B markers. AST 8 IU/L; ALT 16 IU/L (03/2011) and remained normal.

Table 1. Right Heart Catheterization Parameters Before and After Occlusion (5 Minutes) of AV Fistula[a]

	Pre-Occlusion	Post-Occlusion
RA	16/14 (12) mm Hg	
RV	86/8 (15) mm Hg	
PAP	90/34 (56) mm Hg	88/31 (53) mm Hg
PCWP (mean)	10 mm Hg	11 mm Hg
CO/CI (TD)	6.24/3.27 L/min	4.89/2.56 L/min
CO/CI (Fick)	8.03/4.20 L/min	6.28/3.29 L/min
PVR	577 dyne sec/cm^5	687 dyne sec/cm^5
MVO2	70% on 2 L/min	63% on 2 L/min

[a]Abbreviations: RA: right atrium; RV: right ventricle; PAP: pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; CO/CI: cardiac output/cardiac index; PVR: pulmonary vascular resistance; MVO2: mixed venous O2.

He was restarted on macitentan but noted no improvement in DOE/SOB. Selexipeg was added and discontinued because of intolerable headache. Eventually, the patient was started on epoprostenol (Veletri), but up-titration was limited by hypotension even with addition of midodrine. The patient continued to deteriorate, and he suffered multiple hospitalizations because of falls, weakness, and fluid overload. Repeat RHC now demonstrated elevated PCWP that responded to dialysis. He unfortunately died after a fall.

DISCUSSION

Pulmonary hypertension (PH) secondary to high cardiac output from an AVF is an under-appreciated but well-described entity in patients with ESRD undergoing hemodialysis (WHO Group 5)[1]. It is usually difficult to diagnose as an isolated, major contributing factor to elevated pulmonary pressures.

It has previously been reported that ESRD patients treated with chronic hemodialysis via arteriovenous access/fistula develop cardiovascular complications including vascular calcification, cardiac-vascular calcification, and atherosclerotic coronary artery disease. Using Doppler echocardiography, pulmonary hypertension and an increase in cardiac output has been reported in 40% of ESRD patients on chronic hemodialysis via arteriovenous access (Abassi et al).[2] Temporary closure of the arteriovenous access and successful kidney transplantation have resulted in a decrease in pulmonary artery pressure, sometimes to the normal range. It has been postulated that the pulmonary circulation in chronic hemodialysis patients may be in a vasoconstrictive state because of metabolic and hormonal derangements. The increase in pulmonary arterial pressure and cardiac output is most likely related to the large size of the arteriovenous access and subsequent increased flow through it, or to altered vascular resistance as a result of local vascular tone and function resulting from an imbalance between vasodilators such as nitric oxide and vasoconstrictors such as endothelin-1. As described by Abassi et al,[2] ESRD has been associated with reduced production of nitric oxide and enhanced synthesis of endothelin-1 by pulmonary vasculature resulting in pulmonary vasoconstriction. Formation of AV access results in increased cardiac output, which worsens existing PH or precipitates PH. PH then worsens with initiation of dialysis. Decreased nitric oxide production and intact endothelin-1 production, the latter a known powerful mitogen, appears to be associated with reduced survival.[2]

Increased endothelin-1 activity has independently been reported in uremia and therefore the possibility that local concentrations of endothelin-1 are enhanced in the pulmonary tissue of hemodialysis patients with PH cannot be excluded. Therefore, the presence of both uremia and arterio-venous access mediated cardiac output elevation is thought essential for development of PH. This type of PH has been demonstrated to be almost completely reversible following reduction in cardiac output or the uremic state (Clarkson in Nakhoul et al).[3,4]

Anemia and fluid overload are often present in ESRD patients and may also contribute to the increase in pulmonary arterial pressure and high cardiac output. Extraosseous pulmonary calcification is found in ESRD patients on chronic hemodialysis. Calcifications can occur in the heart, lungs, and kidneys. In the lungs, calcium deposits have been found in the interstitium of the alveolar septum, bronchial walls, large airways, and pulmonary vessels; these metastatic calcifications are thought to contribute to the pathogenesis of PH in chronic hemodialysis patients by causing increased stiffness of the pulmonary vasculature.

Renal transplantation has been associated with reversibility of PH. Alternatively, surgical reduction of outsized arteriovenous access has been beneficial in instances in which reduction in cardiac output and PH have been demonstrated following temporary closure of the AVF. Finally, peritoneal dialysis may be an alternative for some patients.

Most commonly, however, the PH in these patients is related to diastolic dysfunction (HFpEF), chronic volume overload from inadequate dialysis, and secondary hyperparathyroidism. Secondary hyperparathyroidism is highly prevalent in PH, might be related to low levels of vitamin D, and might contribute to bone and possibly pulmonary vascular disease. Formation of intravascular pulmonary lesions and calcifications have been associated with secondary hyperparathyroidism.

ElSaid et al[5] found that PH is highly prevalent among patients on hemodialysis and may be associated with mild to moderate impairment of cardiac systolic function. In this clinical scenario, PH seems related to chronic fluid volume overload and increased interdialytic weight gain.

Baseline and regular echocardiographic evaluation of PASP in patients on hemodialysis is recommended. Careful assessment of volume state along with encouraging patients to limit interdialytic weight gain may help reduce PASP.

DiLullo et al[6] report a 40% prevalence of elevated pulmonary pressures in hemodialysis patients from both central venous catheter and AVF vascular access. It is proposed that secondary PH in ESRD is related to impairment in pulmonary circulation, chronic volume overload and increased levels of cytokines and growth factors such as fibroblast growth factor, platelet derived growth factor, and tissue growth factor-beta leading to fibrosis. In addition, endothelial dysfunction, lower levels of nitrous oxide species, and increased levels of serum endothelin and fibrin stores result in complete obliteration of pulmonary vessels by endothelial cells. Proliferation of myointimal vessel wall, intimal laminated fibrosis, thrombosis and obliteration of arteries are typical pathologic features of disease progression.

The RV has thin muscular walls and lower blood pressure and is not able to generate high vascular pressures. Tricuspid regurgitation and further right heart overload develop because of PH secondary to pressure overload and loss of right chamber distensibility. Interestingly, in an overloaded RV resulting from such physiological stresses, a single hemodialysis session has been shown to significantly improve RV function as measured by tricuspid annular plane systolic excursion (TAPSE).[6]

Diagnosis of PH is suggested by the following echocardiographic findings, including right heart chamber dilation, D-shape of the right ventricle caused by flattening of the interventricular septum, absence of inferior vena cava inspiratory collapse, and small or absent *a* (atrial) wave, the latter on M-mode transthoracic echocardiography.

Doppler evaluation is quantitative and allows assessment of pulmonary arterial pressure by tricuspid and pulmonary regurgitation speed assay. Tricuspid regurgitation speed (V_{TR}) is evaluated by 4-chamber echocardiographic apical view with ultrasound probe following transvalvular flow to collect regurgitation volume. V_{TR} reveals the systolic pressure gradient between the 2 right heart sections. If right atrial pressure (RAP) is added, PASP is obtained: PASP = $4(V_{TR})^2$ + RAP. RAP is estimated using inspiratory collapse of the inferior vena cava (IVC) diameter on transthoracic echocardiography. If IVC diameter deceases by > 50% with inhalation, right atrium pressure is < 10 mm Hg; if IVC inhalatory collapse is < 50%, right atrium pressure is > 10 mm Hg. If the right atrium is dilated (area > 15 cm^2), RAP is at least 15 mm Hg in situations without pulmonary valve stenosis or any other mechanical obstruction to right ventricular outflow.

Right ventricular function may be assessed by measuring upper-caudal excursion capability of the TAPSE. TAPSE can be assessed with M-mode, measuring the distance of tricuspid annular movement between end-diastole to end-systole. A compliant right ventricle allows wide excursion of the tricuspid annulus, while this is prevented or restricted in progressive right heart failure. TAPSE can be used in atrial fibrillation and tachycardia.[7]

Moreover, PH is an independent risk factor for mortality and morbidity for ESRD patients on hemodialysis via an AVF. Measures to decrease fistula-related PH and increased cardiac output, including shunt reduction, ligation of fistula, adoption of peritoneal dialysis, or expediting renal transplantation, should be considered. Raina[7] further reports that pulmonary hypertension in chronic kidney disease is typically associated with left heart disease (WHO Group 2).[1] Further contributing factors to pulmonary venous congestion include left ventricular hypertrophy, systemic hypertension, ischemic heart disease, and left ventricular diastolic dysfunction. Pulmonary arterial hypertension (WHO Group 1)[1] is not common in this population. A mixed phenotype of pulmonary vascular disease with pulmonary venous hypertension has been described in this population. PH has been described as an independent predictor of mortality in chronic kidney disease patients, especially those receiving renal replacement treatment. PH has been associated with early renal allograft dysfunction and reduced survival after renal transplantation, and for these reasons significant PH is a relative contraindication to renal transplant.

Teaching Points

1. A hyperdynamic circulatory state from AVF in ESRD patients should be considered in the differential for causes of PH. Improvement in cardiac output and/or pulmonary pressures after obliterating or bypassing the fistula confirms this hypothesis.[8]
2. Measures to decrease fistula-related PH, including shunt reduction, fistula ligation, peritoneal dialysis, or kidney transplantation, should be considered.
3. Early screening for PH by echocardiography in ESRD patients may enable early intervention such as aggressive treatment of anemia and fluid overload status

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"Just Do It": Practical Aspects of Pulmonary Rehabilitation Programs

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WHAT IS PULMONARY REHABILITATION?

Pulmonary rehabilitation (PR) is a specialized physical therapy program to improve the quality of life for patients who have symptoms from chronic lung disease. The American Thoracic Society offers a formal definition of PR as a:

> . . . comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors.[1]

Although PR was originally developed to address the needs of patients with the most common forms of lung disease (which result from smoking),[2] the goals of PR can be applied to help patients with other types of lung disease, including patients with pulmonary hypertension.[3]

WHAT ARE THE IMPORTANT COMPONENTS OF A PULMONARY REHABILITATION PROGRAM?

While a significant portion of the program is devoted to exercise sessions for improving physical conditioning, PR provides an opportunity to optimize patients' self-management skills to reduce the frequency and severity of pulmonary symptoms, reduce the risk for hospitalization, and help address anxiety and depression that may result from their chronic lung disease. This helps patients to engage in daily activities, participate in events with family and friends, and return to their previous level of function after a hospitalization or recovery from an exacerbation of their pulmonary condition. The benefits from PR are not just from patient contact with the medical staff, but also from supportive interactions with other patients enrolled in the program.

Pulmonary rehabilitation programs are staffed by a multidisciplinary team. This is important for tailoring the program to a patient's specific needs. The core members of a PR program often include doctors, nurses, and respiratory therapists. Most programs will also integrate additional staff, including exercise physiologists, physical and occupational therapists, nutritionists or dieticians, and psychologists or social workers.

Although regular visits to doctors remain important to define a patient's medical treatment plan, PR offers a supportive environment to "fill the gap" and empower patients with skill and confidence needed for managing their chronic lung disease. After an initial visit, an individualized treatment plan is created by input from the multidisciplinary team and tailored to the patient's specific needs. Some of the common topics addressed by PR include:

- Education to improve the patient's understanding of their chronic lung disease;
- Review breathing techniques and energy conservation strategies;
- Review techniques and devices to support airway mucus clearance;
- Address questions regarding medications for maintaining stable chronic lung disease;
- Review how and when to use home oxygen (O_2) therapy and other respiratory devices;
- How to recognize symptoms that indicate deterioration of his or her chronic lung disease;
- Identify and reduce the impact of depression, anxiety, and other psychosocial stressors that are more common among patients with chronic lung disease;
- Review and address questions about the action plan recommended by the patient's local doctors.

WHY IS PULMONARY REHABILITATION USEFUL?

When patients start to experience symptoms from chronic lung disease, there is a natural tendency to hold back or slow down because they do not feel well, avoiding activities that cause shortness

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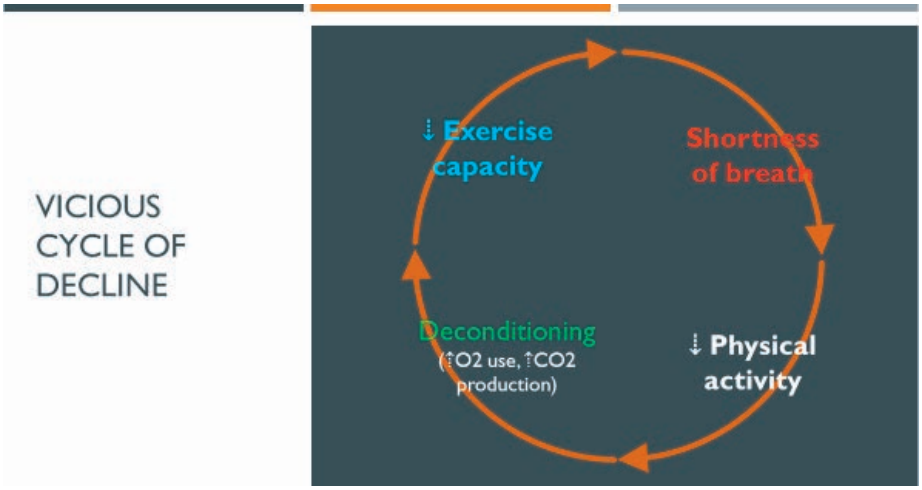

Figure 1: Patients who experience symptoms of chronic lung disease, such as pulmonary hypertension, will often refrain from physical activity. When patients become less active and stop exercising, this leads to deconditioning, meaning that their muscles become less efficient, and this places even more demands on their breathing. This results in a negative impact on their exercise capacity, and they will experience shortness of breath at even lower workloads.

of breath. When patients become less active, this leads to deconditioning, meaning that their muscles become less efficient, using more O_2 and producing more carbon dioxide (CO_2) during any activity, and this places even more demands on their breathing.

As patients become more deconditioned, they will experience shortness of breath at even lower workloads, creating a vicious downward spiral of deterioration (Figure 1). Additionally, how patients respond to stress and discomfort will also influence their behavior, meaning that some patients become anxious when they are short of breath, and this causes them to breathe faster than necessary and adds even more to their shortness of breath.

Through monitored exercise sessions that are tailored to a patient's specific limitations and needs, PR can help patients to overcome deconditioning, reducing the demands that physical activity imposes on their heart and lungs. With improvements in exercise tolerance and reduced shortness of breath in response to physical activity, many patients will feel more confident about re-engaging with friends, family, and other activities they may have avoided or abandoned when they were not feeling well. In turn, PR can help patients be less worried and distracted by their lung disease and function better in the real world.

ARE THERE ANY SPECIAL CONCERNS FOR PATIENTS WITH PULMONARY HYPERTENSION?

Patients with PH have special reasons for impaired exercise capacity. Although different patients may have different reasons for having PH, the main symptoms and problems that patients have are due to increased blood pressure in the lungs (the definition of PH). On average, a person's total blood volume is approximately 1 gallon, and it is the heart's job to pump blood out from the left ventricle to the other major organs through the arteries. The blood then returns back to the heart through veins, and it is the job of the right ventricle to pump the same 1 gallon of blood per minute through the lungs.

For patients with PH, the right ventricle must work harder to pump blood through the lungs, and when they engage in physical activity, either through exercise or just from their routine daily activities, this increases the demand to deliver more O_2 to the muscles of the arms and legs and a need for the lungs to get rid of additional CO_2 being produced by the muscles (Figure 2). Pulmonary hypertension will also cause some patients to have low O_2 levels, both at rest and during physical activity, causing the heart to work even harder to pump more blood with less O_2 in it to support the muscles and other major organs. As a patient's PH worsens, the right ventricle might not be able to keep up with this work load, causing shortness of breath, leg swelling, and early fatigue during physical activity.

If a patient's heart cannot keep up with the increased workload caused by PH, then patients will start to show signs of right heart failure, which means that the right heart is unable to pump enough blood through the lungs to meet the needs of other major organs, causing other symptoms including:

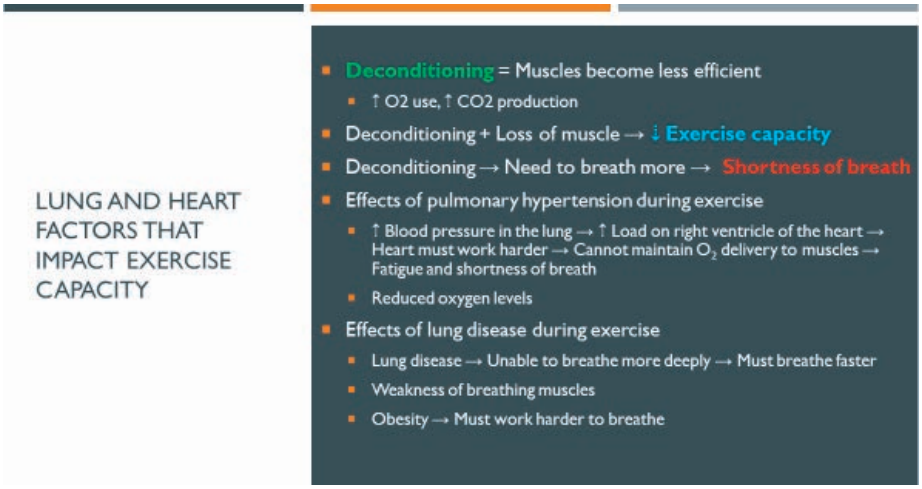

Figure 2: In addition to the negative effects from deconditioning, pulmonary hypertension will impose an additional load on the right ventricle on the heart, exacerbating the degree of fatigue and shortness of breath during physical activity. These problems are made worse by coexisting lung disease, which magnifies the work of breathing needed to support the metabolic demands from exercise.

- Hypotension
- Tachycardia
- Syncope and pre-syncope
- Reduced urine output and other signs of kidney damage
- Nausea or abdominal pain

For these reasons, it is important for PH providers to assess and document that the patient's PH is stable and they do not have signs of right heart failure before starting an exercise program. This is also why it is often useful for PH patients to begin to exercise under the supervision of a PR program. The PR staff will routinely monitor patients for signs of hypotension, tachycardia, hypoxia, chest pain, or syncope. Many standard rehabilitation orders include the administration of nitroglycerin for chest pain. This order should be removed for PH patients receiving sildenafil, tadalafil or riociguat due to a drug interaction.

For those patients who have PH that is caused by another lung disease, such as emphysema or pulmonary fibrosis, this creates even more difficult problems. When patients with both PH and another lung disease experience shortness of breath, they are unable to simply take deeper breaths; they can only breathe faster when short of breath or when trying to exercise. By breathing faster than normal even during low level physical activity, this causes their breathing muscles to need more O_2 and produce more CO_2, which in turn places more demands on their lungs and breathing muscles.

Patients with PH due to another lung disease often have great difficulty maintaining normal O_2 levels and require very high flow O_2 during physical activity. This is often another reason for patients to start exercising under the supervision of a PR program where very high flow O_2 is available. The combined effects of deconditioning, PH, and lung disease cause patients to have very limited exercise capacity, and sometimes a modified exercise program using interval training should be considered until the patient can tolerate longer intervals of physical activity.

Pulmonary rehabilitation programs also offer an opportunity for PH patients to meet with a nutritionist to address individual needs, including reviewing low sodium options for patients with leg edema or other signs of fluid overload, diet modifications for weight control, and review nutritional strategies to preserve muscle mass for patients who have very severe lung disease.

WHO CAN ENROLL IN PULMONARY REHABILITATION?

Government regulations established by Centers for Medicare & Medicaid Services outline how PR for patients with chronic obstructive pulmonary disease (COPD) is supported by health care coverage. These guidelines outline how PR is covered by Medicare for patients with moderate to very severe COPD. However, coverage for other lung problems is determined on a case-by-case basis, and coverage may differ depending on insurance plans. For cases where insurance coverage is limited, it may be helpful to have a discussion with the PR program about the appropriate diagnosis and billing codes that could be used to maximize reimbursement. The most common lung problems addressed through PR include:

- COPD (which includes emphysema and chronic bronchitis);
- Interstitial lung disease (including idiopathic pulmonary fibrosis);
- Sarcoidosis;
- Pulmonary hypertension;
- Bronchiectasis;
- Lung cancer and lung cancer surgery;
- Lung volume reduction surgery;
- Before and after surgery for lung cancer or lung transplantation.

Referrals to the PR program must be made by a signed physician order. This must be accompanied by medical records from the past 6 to 12 months that include physician notes, chest x-ray or computed tomography (CT) scan report, pulmonary function tests, electrocardiogram, and bloodwork results. Additional details regarding a patient's PH may also be requested, such as reports from echocardiogram and right heart catheterization.

For patients with certain medical problems, such as diabetes, a special action plan may need to be discussed with the patient's primary doctor. Exercise training is a healthy approach to lowering blood sugar levels. Patients with diabetes may be asked to check their blood sugars before and after each PR session, and it will be necessary for the patient to review this information with their primary doctor first to see if they should change how they take their diabetes medications on the days they attend PR.

For patients who do not have access to local PR programs, cardiac rehabilitation programs or supervised exercise by physical therapy programs can be considered if insurance coverage is available.

OPTIMIZING USE OF PULMONARY REHABILITATION

Limited Awareness

Pulmonary rehabilitation has proven to be an important and safe treatment option for patients with chronic lung disease. Even for patients with severe PH, successful completion of PR can improve a patient's exercise capacity and quality of life, reduce shortness of breath and fatigue, and possibly even improve the management of their PH.[4] Although PR is considered to be part of the standard of care for patients with symptomatic chronic lung disease, medical authorities are concerned that many patients who would qualify and benefit from PR are not receiving PR as part of their PH management plan.[5] Raising awareness in patients and their doctors of the availability of PR would be one way to maximize the benefits to patients with PH.

Health Care Coverage Limits

Similar to how many dental insurance plans set a lifetime limit for orthodontic treatment (for example, braces), some health insurance plans set a lifetime limit for PR coverage, even though, from a patient's perspective, they may need PR for what is usually a lifelong condition, such as PH or COPD. For patients who experience frequent hospitalizations related to their lung disease and have a lifetime limit for PR coverage, the patient must review alternative approaches with their primary provider and PR program, including transitioning

to a phase 3 pulmonary maintenance program (PMP), described below.

Pulmonary Maintenance Program

It remains important for patients to continue to exercise routinely and maintain health-enhancing activities (low sodium diet, proper use of O_2, refraining from tobacco use) gained through the standard outpatient phase 2 PR program. To assist with this, many PR programs offer a phase 3 PMP. This allows patients continued access to the PR equipment and staff at a lower cost, particularly if they are unable to make arrangements either on their own or through a local exercise facility. Pulmonary maintenance programs are usually intended for recent "graduates" from a standard phase 2 PR program, where the patient is familiar with the exercise procedures and equipment and they have been observed long enough to confirm that they are motivated and capable to exercise safely with less direct supervision.

Logistics of Pulmonary Rehabilitation

Since the inauguration of the first PR programs, patients referred to PR, on average, have become older and have more medical problems. This imposes new challenges to successful participation in PR. Of course, doctors should take care to help patients enroll in a program closest to their home or place of work; the American Association for Cardiovascular and Pulmonary Rehabilitation maintains a directory: https://www.aacvpr.org/Resources/Resources-for-Patients/Pulmonary-Rehab-Patient-Resources.

To ensure that patients can maximize the benefits gained from PR, patients are encouraged to participate at least 2 days per week. Many patients have additional demands on their time and may need to make time for other medical visits, family events, planned trips, and unplanned acute illness. One specific example: a patient who requires outpatient dialysis must make sure that their dialysis schedule is compatible with the available PR sessions. Patients who rely on public transportation, mobility services, or require additional assistance to bring them to PR must take care to make arrangements in advance.

Formal PR as an adjunct therapy for PH is now embedded in the guidelines for standard PH care. To successfully enroll and complete PR, careful collaboration between the PH patient, PH providers, and the PR program is required for safety, efficacy, adherence, and insurance coverage.

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