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.

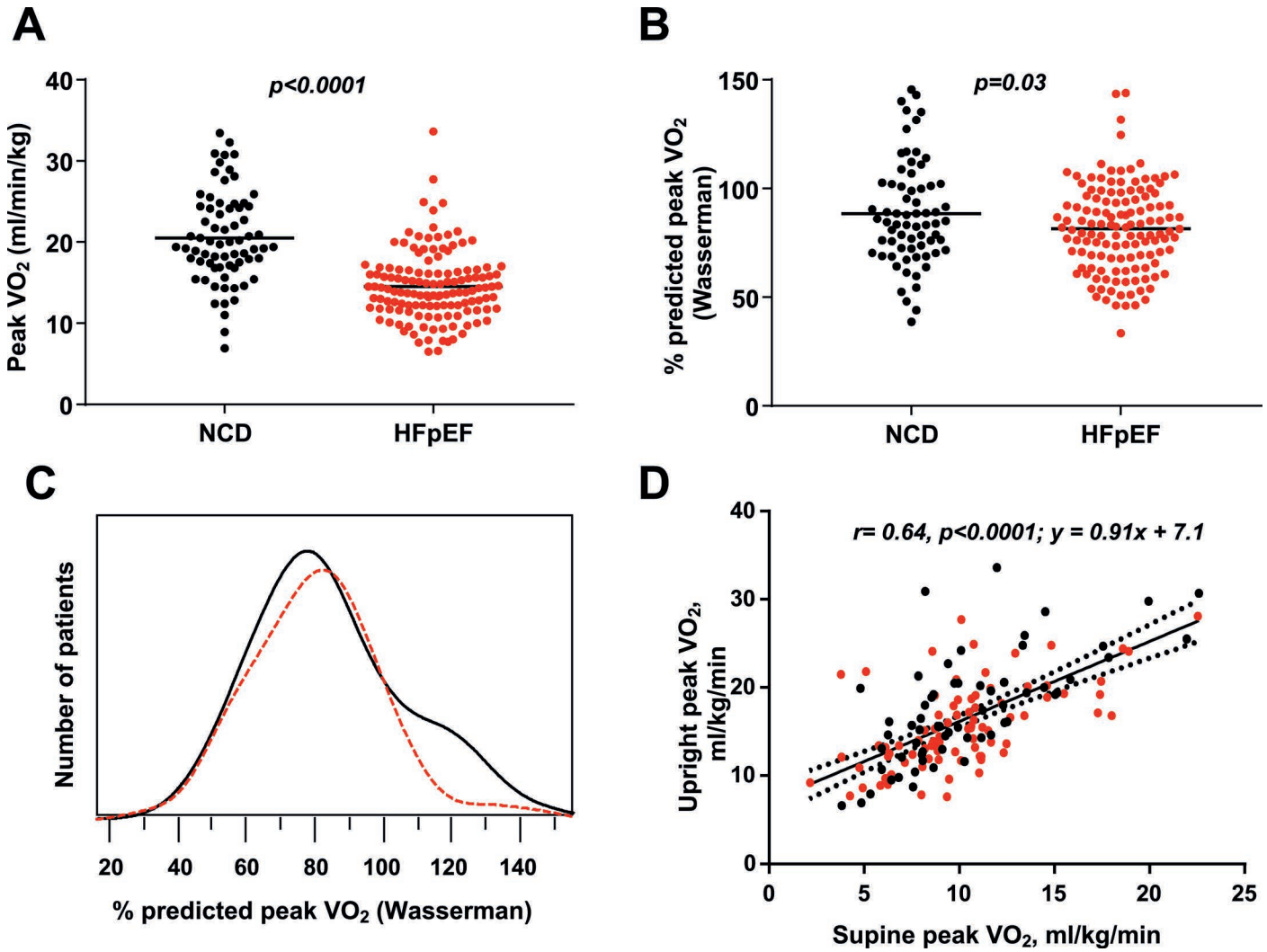

Figure 1: Percent predicted maximal oxygen consumption ($\dot{V}O_2$peak) among patients with unexplained dyspnea. Although there were significant (P = 0.03) differences in mean $\dot{V}O_2$peak between patients with noncardiac dyspnea (NCD) and heart failure with preserved ejection-fraction (HFpEF), 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.

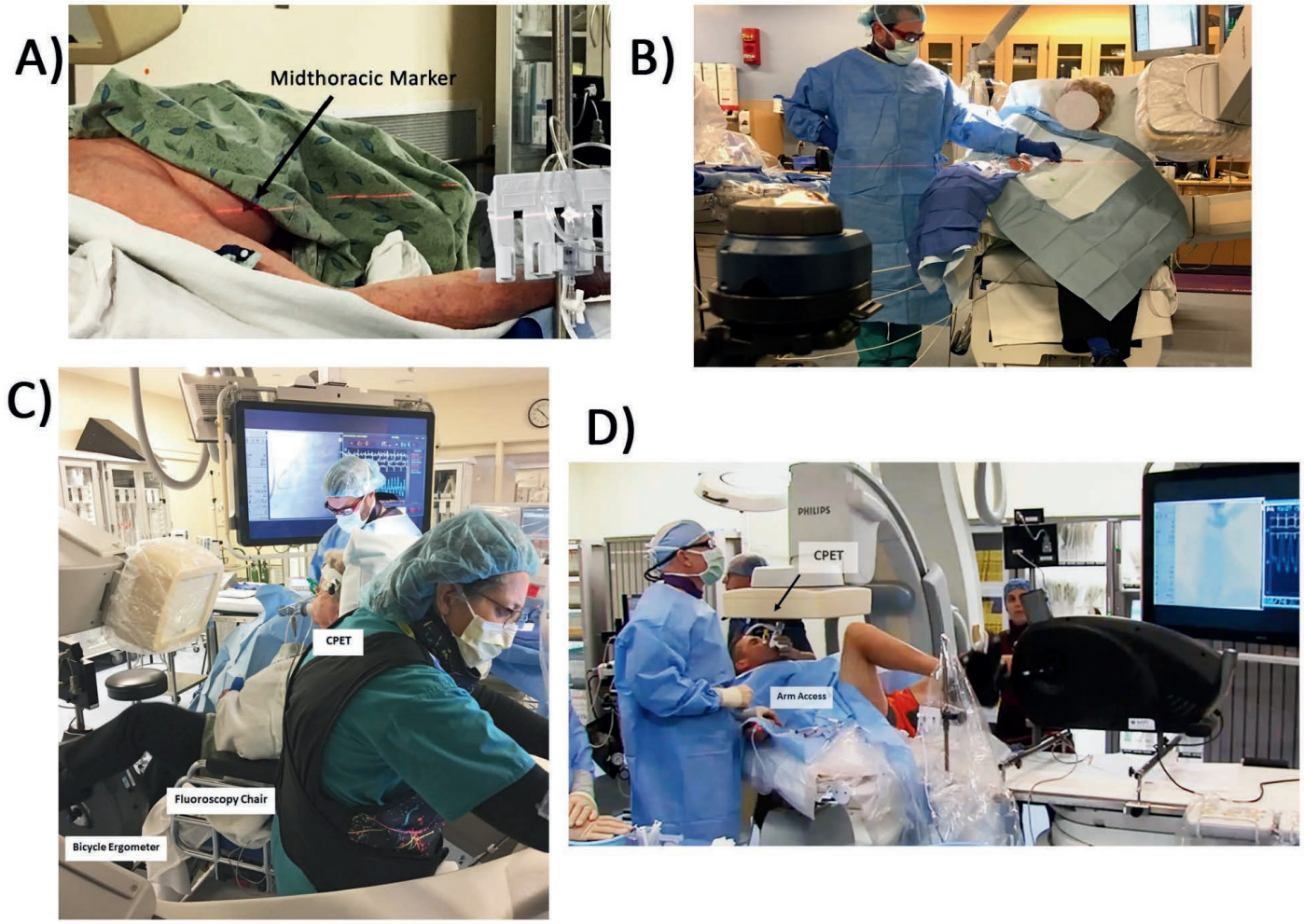

Figure 2: Catheterization lab setup for supine and upright invasive cardiopulmonary exercise testing. (**A**) Supine zeroing is done at the midthoracic level by measuring ½ the anteroposterior diameter of the chest. A laser is then used to bring the transducer stopcock to the midthoracic mark.[40] (**B**) 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

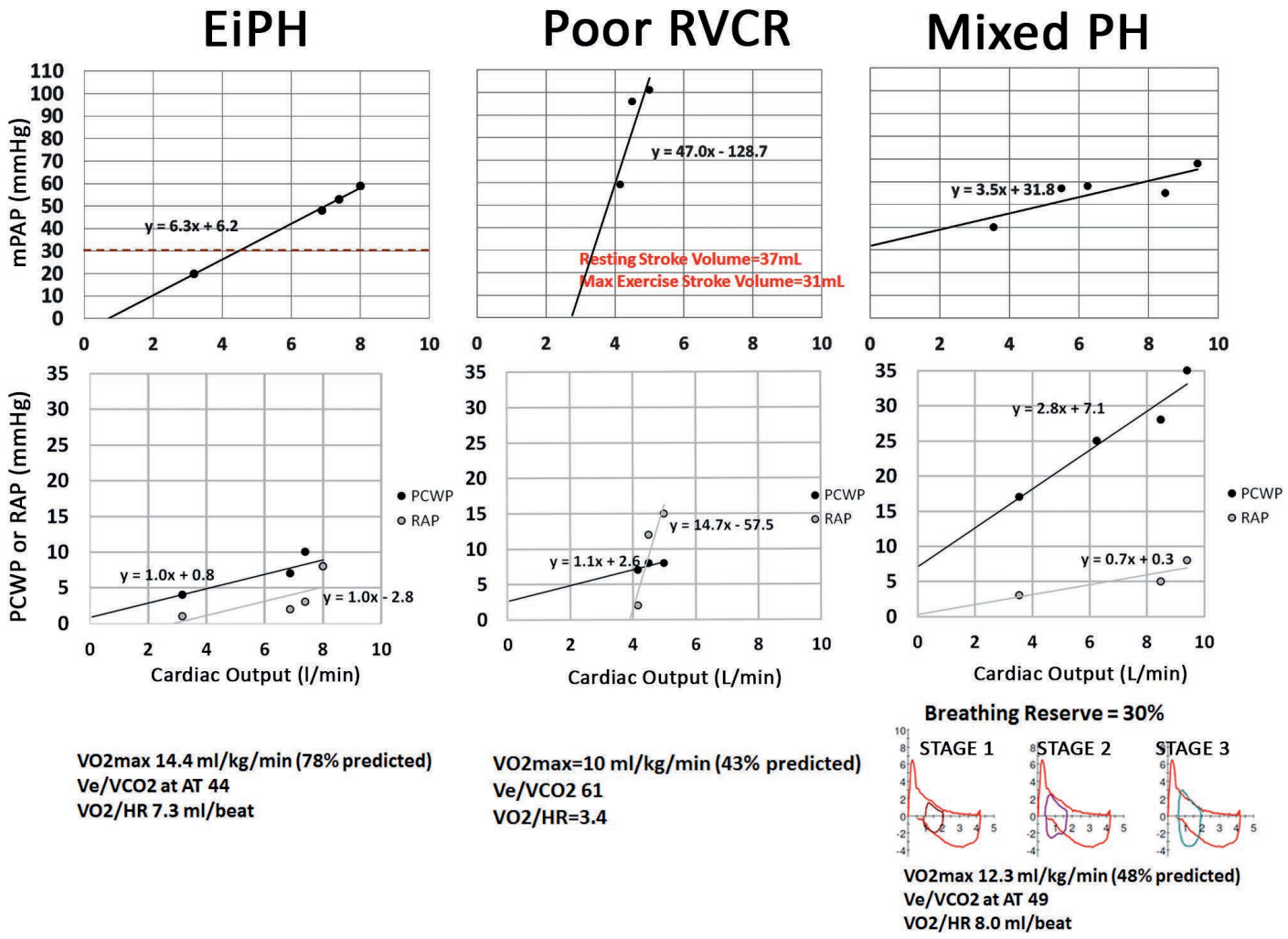

Figure 3: The utility of invasive cardiopulmonary exercise (iCPET) in the phenotyping of patients with pulmonary vascular disease. (**Left column**) Exercise-induced pulmonary hypertension (EiPH) is diagnosed by iCPET by mPAP at exercise >30 mm Hg (horizontal red line), a tPVR > 3 WU, normal PCWP, and 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

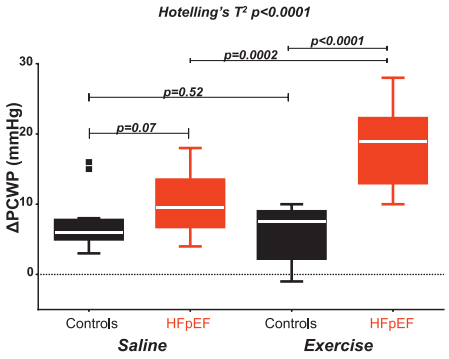

Figure 4: Differential effects of fluid loading versus exercise on pulmonary capillary wedge pressure (PCWP) in control patients versus heart failure with preserved ejection fraction (HFpEF). Although fluid loading and exercise show a similar change in controls, exercise showed a greater change in HFpEF 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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