

# Chapter 11

## Cardiopulmonary Exercise Testing in Pulmonary Hypertension

David M. Systrom and Aaron B. Waxman

**Abstract** Early and accurate diagnosis of pulmonary vascular disease is important given the high mortality of untreated pulmonary hypertension. The development of cardiopulmonary exercise testing (CPET) has allowed an early diagnosis of PAH in “at risk” patients or those with suggestive clinical findings. CPET can quantify the degree of exercise impairment, and rule out a pulmonary mechanical limit to exercise. It can also be used to monitor disease progression and response to treatment. CPET generally consists of an incremental symptom-limited cycling or treadmill exercise test with measurements of ventilation and pulmonary gas exchange. Noninvasive testing is done with continuous 12-lead ECG, cuff blood pressure monitoring and pulse oximetry. Invasive CPET adds arterial and pulmonary artery catheters for blood gas, pH and pressure measurements. CPET when used in the context of a diagnostic algorithm, can confirm the diagnosis of exercise-induced PH, distinguish between pulmonary arterial and venous hypertension, and rule out confounders such as impaired systemic O<sub>2</sub> extraction. CPET may be used alone or combined with other modalities, such as transthoracic cardiac Doppler echo and MRI. Recent expert consensus statements suggest CPET is useful in the diagnosis, management and risk stratification of PH. This chapter provides an overview of the history of CPET, describes how measurements are obtained and interpreted, and discusses its use in diagnosis and monitoring of pulmonary hypertensive diseases including exercise-induced pulmonary hypertension and pulmonary hypertension associated heart and lung disease.

**Keywords** Cardiopulmonary exercise testing • Pulmonary arterial hypertension • Pulmonary hypertension

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## Abbreviations

6MWT	6-min walk test
A-sDO <sub>2</sub>	Alveolar–arterial oxygen tension difference
AT	Anaerobic threshold
BRI	Breathing reserve index
CaO <sub>2</sub>	Oxygen content of arterial blood
CO	Cardiac output
CPET	Cardiopulmonary exercise test
CvO <sub>2</sub>	Oxygen content of venous blood
DO <sub>2</sub>	Oxygen delivery
DO <sub>2</sub> max	Maximum systemic oxygen delivery
eiPAH	Exercise-induced pulmonary hypertension
EOV	Exercise oscillatory ventilation
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduce ejection fraction
ITP	Intrathoracic pressure
IVS	Interventricular septum
LT	Lactate threshold
LV	Left ventricle
LVEF	Left ventricular ejection fraction
mPAP	Mean pulmonary artery pressure
MVV	Maximum voluntary ventilation
OUES	O <sub>2</sub> uptake efficiency slope
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PASP	Pulmonary artery systolic pressure
PCWP	Pulmonary capillary wedge pressure
PETCO <sub>2</sub>	End tidal PCO <sub>2</sub>
PFO	Patent foramen ovale
PH	Pulmonary hypertension
PVD	Pulmonary vascular disease
PVL	Pulmonary vascular limit
PVR	Pulmonary vascular resistance
RA	Right atrium
RAP	Right atrial pressure
RER	Respiratory exchange ratio
RHC	Right heart catheterization
ROC	Receiver operating characteristic
RV	Right ventricle
RVSP	Right ventricular systolic pressure
SVR	Systemic vascular resistance
TPG	Transpulmonary gradient

ULN	Upper limit of normal
VAT	Ventilatory anaerobic threshold
VCO <sub>2</sub>	Carbon dioxide production
VE	Minute ventilation
VE <sub>max</sub>	Minute ventilation at peak exercise
VO <sub>2</sub>	Oxygen uptake
VO <sub>2</sub> max	Maximum oxygen uptake
VT	Tidal volume
WHO	World Health Organization

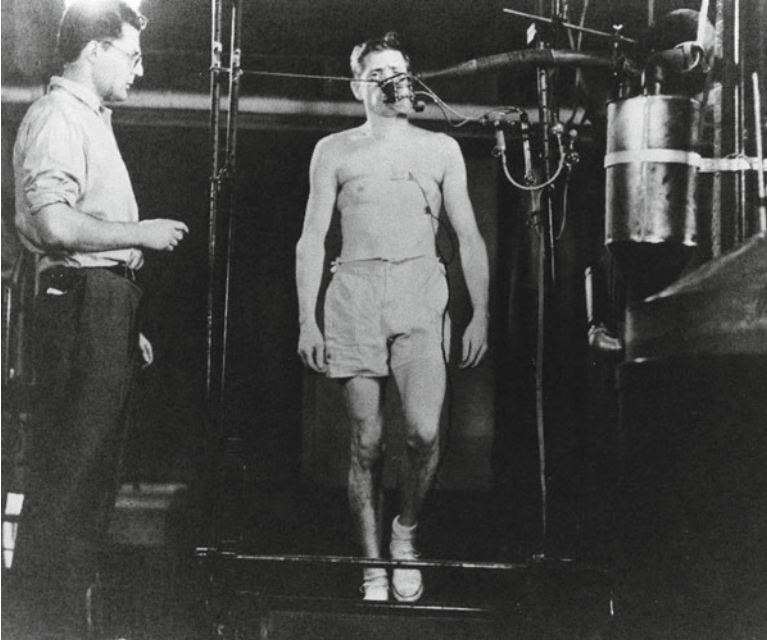
## Introduction

The timely and accurate diagnosis of PH is important given the high mortality if left untreated [1, 2], the availability of increasingly effective medical therapies [3] and a long wait for a donor lung at most transplant centers [4]. The development of cardiopulmonary exercise testing (CPET) has allowed an early diagnosis of PH in “at risk” patients or those with subtle suggestive clinical findings, affording the opportunity to treat patients most likely to benefit and to monitor their response.

PH carries a poor prognosis, with a mortality of about 15 % in 1 year despite modern therapy. The diagnosis of PH is often delayed; the average time from onset of symptoms to diagnosis is approximately 2 years [2]. The delay is due, in part from the nonspecific signs and symptoms of the disease, and the complex, extensive workup necessary to determine a cause of elevated pulmonary artery pressure. Traditional evaluation of resting pulmonary function and gas exchange is insensitive [5, 6], and further contributes to the diagnostic delay. Early PH generally does not cause symptoms at rest and stressing pulmonary vasculature with exercise may be necessary to demonstrate abnormal structure and function [2, 7–10]. An appropriate analogy might be that of coronary artery disease; a resting left heart catheterization identifies severe disease, but milder hemodynamically significant disease requires a functional study for its diagnosis.

Cardiopulmonary exercise testing (CPET) is such a functional test that may elicit early [7] and reproducible [11, 12] abnormalities suggestive of PH. CPET generally consists of an incremental symptom-limited cycling or treadmill exercise test with measurements of ventilation and pulmonary gas exchange [13, 14]. The first CPET done was in the Harvard Fatigue Lab in the 1920s (Fig. 11.1) where many of the basic tenets of normal human exercise physiology were described using measurements of ventilation, pulmonary gas exchange, arterial blood gases and pH as well as noninvasive estimates of cardiac output.

Currently, CPET is subdivided into noninvasive testing (niCPET), done with continuous 12-lead ECG, cuff blood pressure monitoring and pulse oximetry, and invasive CPET (iCPET), which adds arterial and pulmonary artery catheters for blood gas, pH and pressure measurements. CPET may be used alone or combined with other modalities, such as transthoracic cardiac Doppler echo and MRI.



**Fig. 11.1** The earliest known CPET was at the Harvard Fatigue Lab in the 1920s

There is a rapidly growing body of evidence supporting its utility in patients with suspected or confirmed PH. Recent expert consensus statements suggest CPET's is useful in the diagnosis, management and risk stratification of PH [15, 16]. CPET is safe even in established PH [17, 18] Severe PH with exertional syncopal episodes, cardiac arrhythmias, or acute right ventricular failure do, however, serve as contraindications to maximum exercise testing [13].

## Noninvasive CPET

niCPET can be used as a screening test in the patient with unexplained exertional intolerance [14, 19] where a significant percentage of patients will ultimately be shown to have PH [7]. Such patients have generally undergone a time-honored history, physical examination, routine blood work, which are normal or, in the eyes of the clinician, show abnormalities insufficiently severe to explain symptoms. niCPET may also be appropriate in suspected PH, e.g., family members of Group 1 PH, or in "at risk" patients with for example connective tissue disease [20].

niCPET can quantify the degree of exercise impairment, rule in or out a pulmonary mechanical limit to exercise and suggest disorders manifested by abnormal  $O_2$  delivery or subsequent uptake and utilization, including PH. niCPET variables that are useful in assessing the presence and severity of PH are shown in Table 11.1. These variables largely reflect PH-related impairment of  $O_2$  delivery to the exercising

**Table 11.1** Variables in niCPET useful in the assessment of PH

Maximum oxygen uptake
Ventilatory or gas exchange anaerobic threshold (AT)
Ventilatory reserve
Ventilatory efficiency
Arterial O <sub>2</sub> desaturation
PETCO <sub>2</sub> change
Exercise oscillatory ventilation
Oxygen uptake efficiency slope

muscle bed and ventilation-perfusion abnormalities in the lung [17, 21–25]. Additionally, niCPET allows reproducible assessment of functional capacity and treatment efficacy in PH and can predict survival [11, 17, 22, 26–28].

### ***Maximum Oxygen Uptake (VO<sub>2</sub>max)***

Overall fitness is generally assessed by the VO<sub>2</sub>max, expressed as a percent of predicted for the patient’s age, gender and estimate of lean body mass, derived from height [29] VO<sub>2</sub> increases linearly vs. work rate with a slope of approximately 10 mL/min/W in normal subjects [29]. This slope is not affected by age, gender, or training, but is shifted leftward in obese patients and may plateau in more severe heart failure (HF). In the obese patient, in the absence of pulmonary vascular disease, the VO<sub>2</sub> max may be surprisingly well-preserved, but the external work performed on the cycle ergometer is compromised. This results from the oxygen cost of moving heavy legs or respiratory muscle work.

In established PH, VO<sub>2</sub>max decreases [7, 17, 23–25, 28, 30, 31]. Even milder exercise-induced PH depresses VO<sub>2</sub>max compared to normal [7, 10]. VO<sub>2</sub>max correlates inversely with resting pulmonary hemodynamics [17] and may improve with pulmonary vasodilator therapy [27, 32], but this is not uniformly observed [21], perhaps in part because of methodological concerns, but perhaps related to confounding deleterious effects of treatment.

VO<sub>2</sub>max is a powerful predictor of mortality in PAH [33, 34] and a peak VO<sub>2</sub> below 10.4 mL/kg/min has been considered a key criterion for early mortality [22].

### ***Ventilatory (VAT) or Gas Exchange “Anaerobic” Threshold (AT)***

Heavy exercise increases blood lactate concentration, ventilation and VCO<sub>2</sub> relative to VO<sub>2</sub>; the latter can be reliably detected noninvasively with CPET using an iterative least residual sum of the squares of a two-segment log–log plot [35]. For many years the lactic acidemia of exercise was assumed to be secondary to inadequate oxygen

delivery to muscle with resultant increases in “anaerobic” glycolysis to produce ATP. However, skeletal muscle mitochondrial redox state is actually higher when working muscle is producing lactate than at rest, implying that oxygen supply is not the critical factor [36–38]. Likewise, the tight mechanistic link between LT and VAT has been undermined by the fact that the two may be uncoupled experimentally [39–41] and in McArdle’s disease [42] where ventilatory patterns during incremental exercise are normal in the absence of lactic acidemia. Nonetheless, the AT varies with cardiovascular fitness, correlates well with human performance in the field, and remains a useful clinical index.

The VAT occurs at greater than 40 % of the predicted  $\text{VO}_2\text{max}$  in normal individuals, but earlier in cardiovascular disease including PH [17, 43, 44]. The AT correlates inversely with resting pulmonary hemodynamics [17] in established PH.

## Ventilatory Reserve

Minute ventilation (VE) normally rises during incremental exercise as a result of a linear increase in breathing frequency and a hyperbolic increase in tidal volume (VT) [45]. VT reaches a plateau at approximately 50 % of the resting vital capacity, above which the elastic work of breathing is prohibitive [46]. The ratio of VE at peak exercise ( $\text{VE}_{\text{max}}$ ) to the maximal voluntary ventilation (MVV) at rest has been termed the breathing reserve index [47]. A breathing reserve index of 0.70 can be sustained for 15 min in normal individuals, but values above 0.75 are usually not attained even at peak exercise [48].

Ventilation in patients with Group 1 PH may be excessive [49], but because the maximum voluntary ventilation is usually near-normal, relatively normal breathing reserve at peak exercise is usually found [17]. The nCPET can rule out a pulmonary mechanical limit to exercise by comparing  $\text{VE}_{\text{max}}$  to MVV. This is especially important in Group 3 PH where there are both pulmonary vascular and mechanical abnormalities limiting exercise. When an abnormal VAT precedes a BRI of 0.70, pulmonary vascular disease likely limits the patient’s activities of daily living. Conversely, when a BRI of 0.70 precedes the AT, pulmonary mechanics are thought to be rate limiting.

## Ventilatory Efficiency

Normally,  $\text{CO}_2$  elimination by the lungs becomes more efficient during exercise [50]. Anatomic dead space increases because of a tethering effect on conducting airways at high VT. Conversely, during upright exercise, alveolar dead space decreases because of augmented blood flow to the lung apices, giving the net effect of a slight increase in total (physiologic) dead space (VD). However, this effect is more than offset by the increased VT, which produces a decrease in upright  $\text{VD}/\text{VT}$

from 0.45 at rest to less than 0.29 at maximum exercise [50]. Normally, the  $VE/VCO_2$  falls as a result to  $<37$  at the ventilatory threshold [17].

Ventilatory inefficiency is one of the hallmarks of PH during exercise [7, 17, 23–25, 28, 30, 31, 51] and can be identified by an increased slope of the linear phase of  $VE/VCO_2$  or its absolute value at the ventilatory threshold. It has been suggested that the latter is preferable as the slope may be artificially flattened by hyperventilation at rest in anticipation of exercise.

A high  $VE/VCO_2$  during the submaximum domain of incremental exercise is explained by the alveolar ventilation equation:

$$VE / VCO_2 = (k) / (PaCO_2(1 - VD / VT)) . [17]$$

Hyperventilation during low-level exercise is common in PH and usually ascribed to a combination of stretch receptors in the RV and pulmonary outflow track, J receptor stimulation (in HF and interstitial lung disease) and hypoxemic stimulation of arterial chemoreceptors [52]. In addition, alveolar dead space fails to fall normally [17, 53, 54] because of blunted pulmonary vascular distention and recruitment, and, perhaps, pulmonary vasospasm [55].

Thus, the combined influence of two invasively measured variables,  $VD/VT$  and  $PaCO_2$  may make the noninvasive  $VE/VCO_2$  a powerful marker of the abnormal pulmonary vasculature. Using a stepwise regression model using  $PaCO_2$  and  $VD/VT$  at anaerobic threshold as independent variables suggested that variability in  $VE/VCO_2$  at anaerobic threshold was accounted for equally by both. In HFrEF we have demonstrated equal contributions of  $VD/VT$  and hyperventilation to ventilatory efficiency [56].

Reybrouck et al. [54] found that the  $VE/VCO_2$  slope was steeper in patients with PH than the slope in patients with normal mPAP, and a significant correlation between the slope and mPAP and the  $VD/VT$ . In PH,  $VE/VCO_2$  is inversely related to peak cardiac output [55], resting [17], and exercise [57] mPAP's and overall exercise capacity [54, 58]. A sudden rise may suggest dynamic opening of a PFO and right to left shunting during exercise [23].

Ventilatory inefficiency can predict adverse events [59] and is likely a better predictor of survival than  $VO_{2max}$  [22, 34, 60]. Recent work suggests [60] ventilatory equivalent for carbon dioxide at anaerobic threshold  $>55$  identifies patients with an over sevenfold increased risk of death within 24 months and better predicted the clinical outcome compared to  $VO_{2max} < 10.4$  ml/min/kg.

Ventilatory efficiency improves after therapy, including pulmonary vasodilators [27, 61] and lung transplantation [49]. Interestingly  $VE/VCO_2$  slope's change after treatment does not appear to influence survival [62].

### ***Arterial O<sub>2</sub> Desaturation***

In the normal human during incremental exercise, arterial O<sub>2</sub> saturation remains normal and the A-aDO<sub>2</sub> widens due to hyperventilation and a rise in the RER. In PH, arterial O<sub>2</sub> desaturation and/or exaggerated widening of the P(A-a)O<sub>2</sub> is due

both to V/Q mismatching and a diffusion defect induced by a rapid red cell transit time through a poorly compliant and recruitable pulmonary circulation. Prevalence of arterial O<sub>2</sub> desaturation with exercise increases with PH severity [28].

Occasionally, a sudden fall in arterial oxygen saturation heralds the opening of a patent foramen ovale and increased right to left shunting due to elevation of right atrial pressure [23].

Exercise arterial O<sub>2</sub> desaturation is not generally a feature of ambulatory HFpEF or HFrEF. Recent work suggests severe O<sub>2</sub> desaturation is a negative prognosticator for PH [63].

### ***End Tidal PCO<sub>2</sub> (PETCO<sub>2</sub>)***

The PETCO<sub>2</sub> normally rises at the AT, reflecting increased VCO<sub>2</sub> delivered to the pulmonary capillary which is disproportionately “sampled” at lower end-expiratory lung volumes. The negative Pa-ETCO<sub>2</sub> gradient is dependent on normal exercise induced pulmonary vascular recruitment and distension.

As with ventilatory efficiency, pulmonary vascular remodeling or dysfunction impairs this response and alveolar dead space fails to fall normally, diluting the end tidal breath with room air [24, 64]. When PETCO<sub>2</sub> at AT is <30 mmHg and especially <20 mmHg, in a patient with exertional dyspnea of unknown cause, PH should be considered as likely.

It has been shown that the PETCO<sub>2</sub> [28] transition from rest to AT can distinguish between PH and left ventricular dysfunction; PETCO<sub>2</sub> tends to decrease in PAH, whereas the PETCO<sub>2</sub> tends to increase in LVD [20, 64].

Like ventilatory inefficiency, disease severity and survival are predicted by the pattern of change [22]. Oudiz et al. have shown higher PETCO<sub>2</sub> at AT after treating PH after sildenafil [65].

### ***O<sub>2</sub> Uptake Efficiency Slope (OUES)***

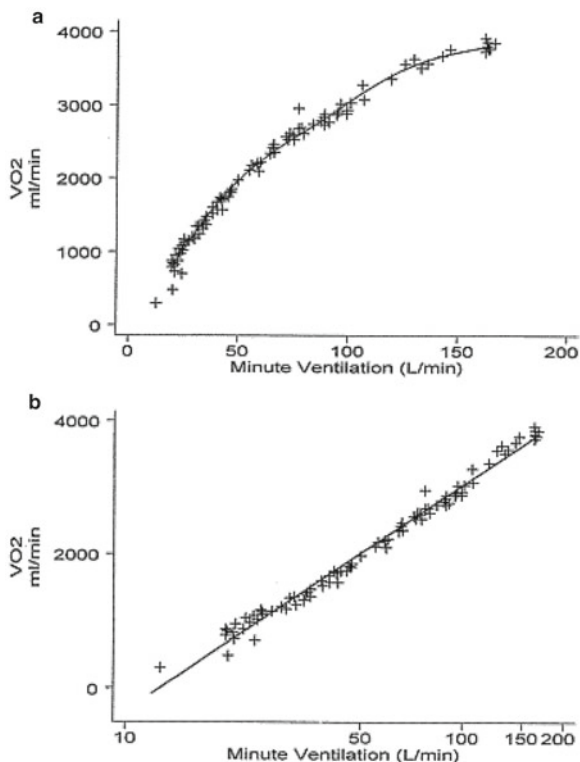
In 1996, Baba et al. proposed a hybrid measurement of oxygen transport and ventilation during exercise as a surrogate for VO<sub>2</sub>max in the pediatric population in whom the latter was difficult to reliably achieve [66]. The OUES is an objective, reproducible measure of cardiopulmonary reserve that does not require a maximal exercise effort. It integrates cardiovascular, musculoskeletal and respiratory function into a single index that is largely influenced by pulmonary dead space ventilation and exercise-induced lactic acidosis.

The OUES is derived from the relation between oxygen uptake ( $\dot{V}O_2$  [ml/min]) and minute ventilation ( $\dot{V}E$  [l/min]) during incremental exercise and is determined by:

$$\dot{V}O_2 = a \log \dot{V}E + b, \quad \text{where } a = \text{OUES (Fig. 11.2).}$$



**Fig. 11.2** O<sub>2</sub> uptake efficiency slope, derived from the semi-log plot (*panel b*) of the rectilinear plot (*panel a*) of VO<sub>2</sub> vs. VE during submaximum exercise [67]



Major factors that influence the OUES are: CO<sub>2</sub> output (derived from muscle aerobic metabolism as well as from the pH buffering function of bicarbonate), arterial pCO<sub>2</sub> set-point, and VD/VT.

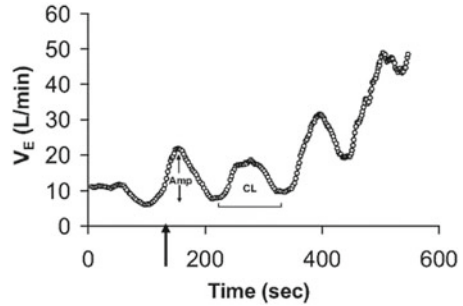
A low OUES predicts poor survival in HF [68] and worse outcome in PH [69]. Ramos et al. performed an ROC curve analysis in PH (area under the curve=0.688 [0.542–0.833],  $p < 0.01$ ), indicating a best OUES cutoff for prognostication of 0.56 L/min/log.

### ***Exercise Oscillatory Ventilation (EOV)***

Cyclic fluctuations in minute ventilation during exercise, called exercise oscillatory ventilation (EOV), have been observed in 19–51 % of patients with HF [70–75]. Exercise oscillatory ventilation is a noninvasive parameter that is easily measurable (Fig. 11.3) during submaximum exercise.

We recently examined iCPET data for EOV in 56 patients with HFReF (mean  $\pm$  SEM age,  $59 \pm 2$  years; left ventricular ejection fraction,  $30 \pm 1$  %) and 19 age-matched control subjects were studied with incremental cardiopulmonary exercise

**Fig. 11.3** Exercise oscillatory ventilation defined as  $\geq 3$  cyclic fluctuations of minute ventilation ( $\dot{V}_E$ ) during exercise with an amplitude  $>25\%$  of the mean trough-to-trough  $\dot{V}_E$  during that interval. *CL* cycle length; *Amp* amplitude [76]

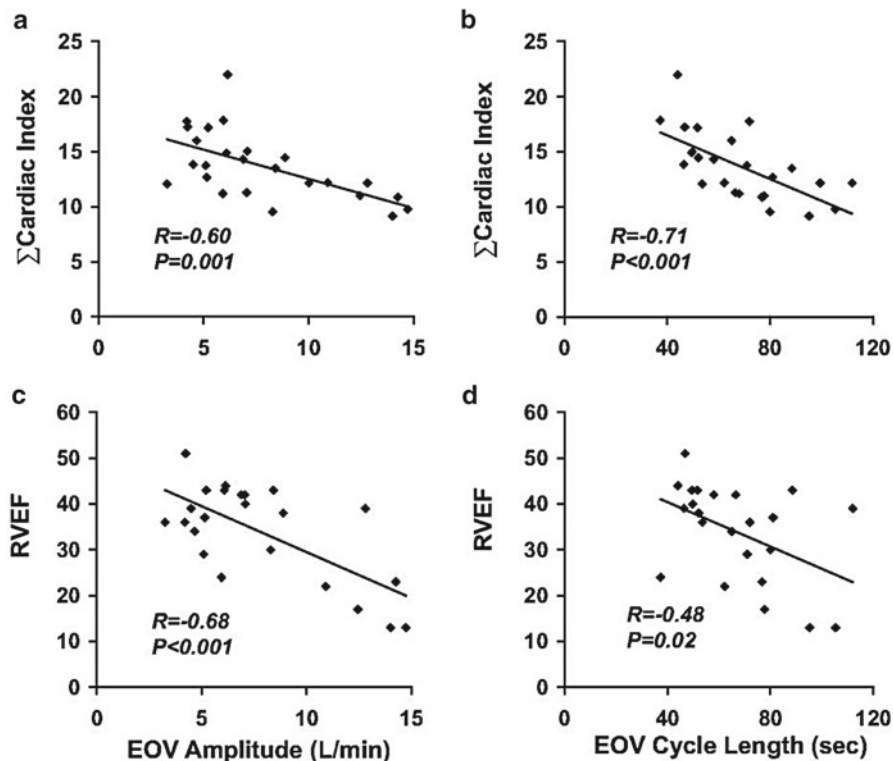


testing. We detected EOv in 45 % of HF (HF+EOV) patients and in none of the control subjects. The HF+EOV group did not differ from the HF patients without EOv (HF-EOV) in age, sex, body mass index, left ventricular ejection fraction, or origin of HF. Univariate predictors of the presence of EOv in HF, among measurements performed during exercise, included higher right atrial pressure and pulmonary capillary wedge pressure and lower cardiac index (CI) but not  $\text{PACO}_2$  or  $\text{PAO}_2$ . Multivariate logistic regression identified that low exercise CI is the strongest predictor of EOv (odds ratio, 1.39 for each 1.0-L/min/ $\text{m}^2$  decrement in CI; 95 % confidence interval, 1.14–1.70;  $P=0.001$ ). Among HF patients with EOv, exercise CI was inversely related to EOv cycle length ( $R=-0.71$ ) and amplitude ( $R=-0.60$ ; both  $P<0.001$ ). In 11 HF+EOV subjects treated with 12 weeks of sildenafil, EOv cycle length and amplitude decreased proportionately to increases in CI. We conclude EOv is closely related to reduced CI, elevated filling pressures and impaired RV contractility (Fig. 11.4) during exercise and may be an important surrogate for exercise-induced hemodynamic impairment in HF patients.

Exercise oscillatory ventilation has emerged as a potent independent risk factor for adverse prognosis in HF [70, 72, 77]. To our knowledge this has not yet been determined for PAH and PH Groups 3–5.

### ***Noninvasive CPET Diagnostic Algorithms for PH***

When used together, patterns of CPET variable changes may increase sensitivity and specificity of exercise testing for the diagnosis of PH [78–81]. Our laboratory validated a classic noninvasive CPET diagnostic algorithm for PH in a population of unexplained dyspnea with direct central hemodynamic measurements [26]. We evaluated 130 consecutive, clinically indicated iPET's whose phenotyping (see below) was performed to determine if PH were present at maximum exercise and limited exercise tolerance (pulmonary vascular limit (PVL) defined as a  $\text{PVR}_{\text{max}} >120 \text{ dyn s cm}^{-5}$  and a maximum systemic oxygen delivery ( $\text{DO}_2_{\text{max}}$ )  $<80\%$  of predicted, in the absence of limiting abnormal pulmonary mechanics or poor effort). We evaluated the accuracy of a published diagnostic algorithm [78] (Fig. 11.5) and sequentially altered branch-point threshold values to maximize accuracy in



**Fig. 11.4** Correlations between exercise oscillatory ventilation (EOV) parameters and cardiac performance; EOV amplitude is inversely related to cumulative cardiac index during exercise ( $\Sigma$ cardiac index; **a**) and right ventricular ejection fraction (RVEF; **c**). In addition, EOV cycle length is inversely related to cumulative cardiac index during exercise (**b**) and RVEF (**d**)

diagnosing PVL. We based threshold values used at each branch point on the 95 % confidence intervals for healthy individuals during exercise [78]. Thus, for the diagnosis of PVL, branch-point values were adjusted in the following order: % predicted  $VO_2$ max, anaerobic threshold as % predicted  $VO_2$ max, breathing reserve maximum, and  $VE/VCO_2$  and anaerobic threshold.

Figure 11.6 shows the changing sensitivity, specificity, and accuracy for PVL when a representative branch point ( $VE/VCO_2$  at anaerobic threshold) was altered systematically. If consecutive branch-point values resulted in identical accuracy, we chose the median value.

In an identical fashion, we determined the utility of isolated peak exercise measurements of  $VD/V'T$  and  $PA-aO_2$  for PVL. We used upper limit of normal values for peak exercise  $VD/V'T$  and  $PA-aO_2$  of 0.28 and 35 mmHg, respectively [78].

The sensitivity of the isolated peak exercise  $VD/V'T$  for PVL was 20 %, with specificity of 85 % and accuracy of 56 %. Similarly, the isolated peak exercise  $PA-aO_2$  had sensitivity for PVL of 24 %, specificity of 92 %, and accuracy of 60 %.

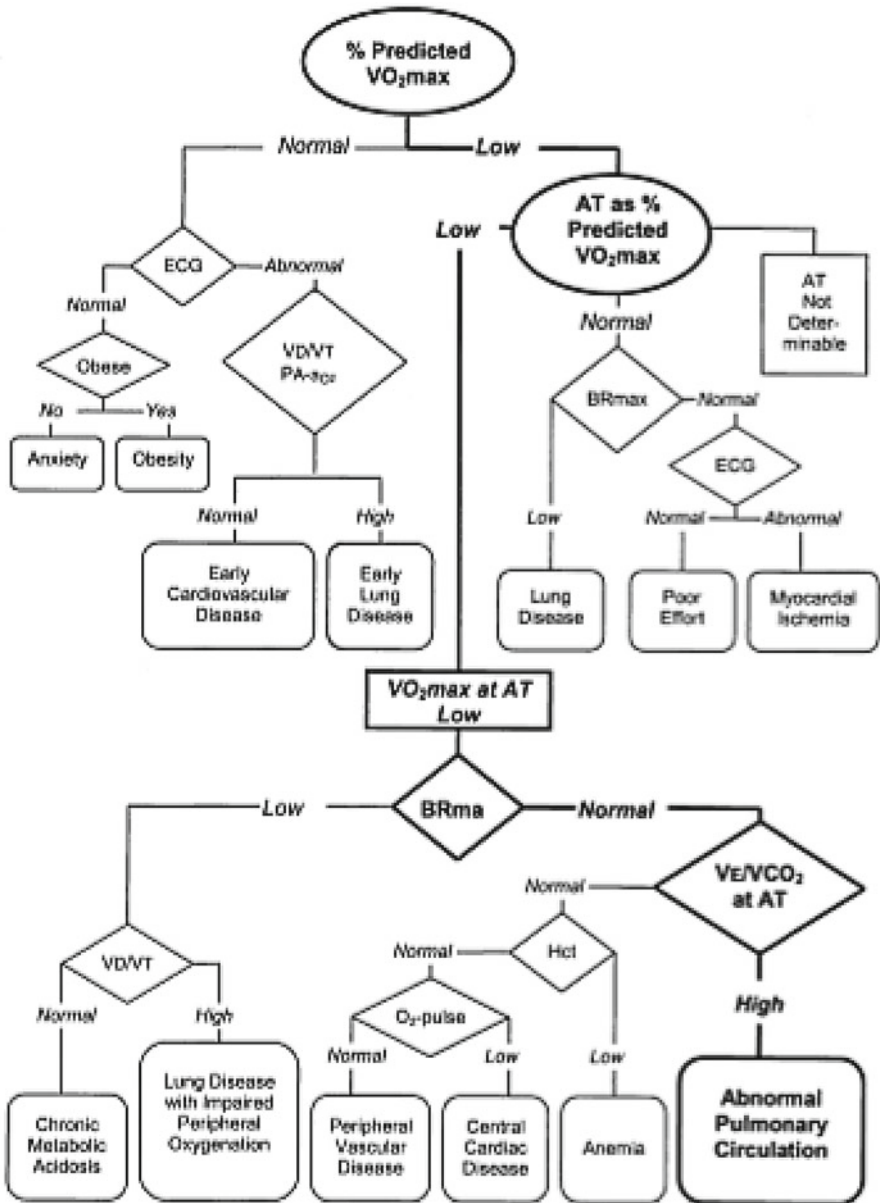
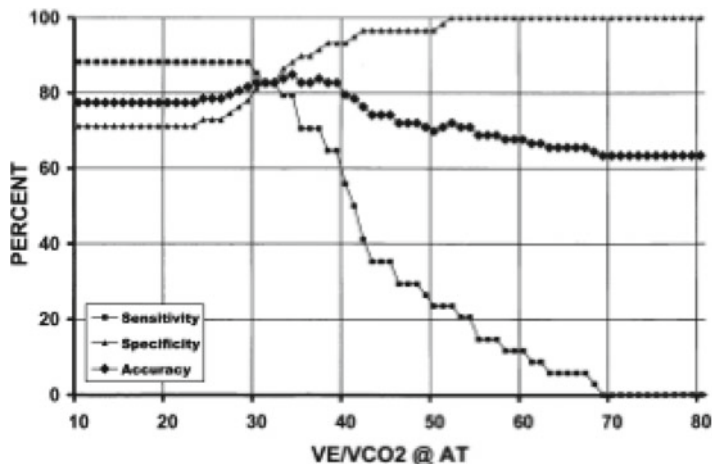


Fig. 11.5 A popular noninvasive CPET diagnostic algorithm with key branch points for PH in **bold**

The noninvasive algorithm’s sensitivity for PVL was 79 %, specificity was 75 %, and accuracy was 76 % (n=93). Systematic alteration of branch-point values improved the algorithm’s specificity and accuracy to 88 % and 85 %, respectively. The greatest improvement in sensitivity for detecting pulmonary vascular limit



**Fig. 11.6** Improvement of accuracy of a noninvasive CPET diagnostic algorithm by adjusting a key branch point ( $VE/VCO_2$ ) cutoff value

resulted from a decrease in the threshold value for  $VE/VCO_2$  at anaerobic threshold; we applied a stepwise linear regression model to this branch point. When  $PaCO_2$  and  $VD/VT$  at anaerobic threshold were denoted as independent variables, the model assigned equal weight to both (standard coefficients = 0.59 and 0.57, respectively,  $p < 0.0001$ ).

A recent study by [20] confirms the utility of a niCPet algorithm for early detection of pulmonary vascular disease in an at risk population. The authors further suggest that one can distinguish right from left sided disease by the addition of  $PETCO_2$  changes from rest to AT.

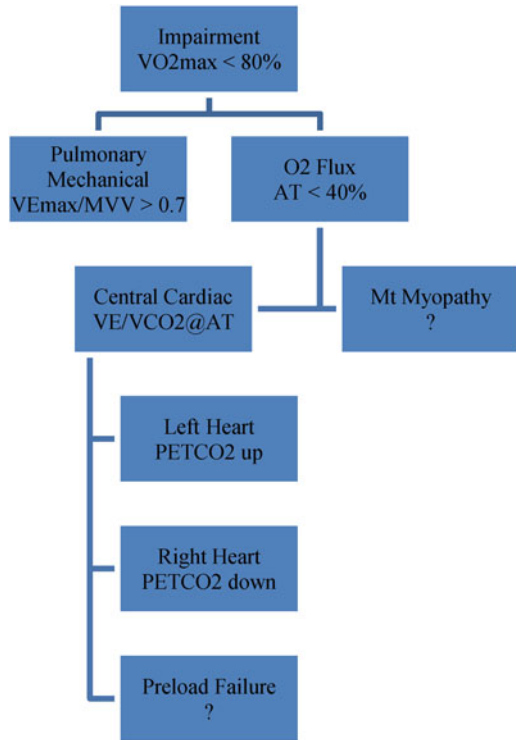
A suggested niCPET for the diagnosis of PH is suggested (Fig. 11.7).

In summary, niCPET is a useful diagnostic modality that can suggest early or mild PH in at-risk patients or those with unexplained exertional intolerance. Confirmation of PH is almost always necessary through right heart catheterization. The remainder of this chapter focuses on combining CPET with RHC hemodynamic measurements.

## Invasive CPET

Measurement of central hemodynamics during exercise has been performed for many years [82–84], but only more recently combined with CPET [85]. In our hands, an iCPET refers to niCPET with the addition of pulmonary and radial artery catheters for pressure measurements and blood sampling.

**Fig. 11.7** A suggested noninvasive CPET diagnostic algorithm. PH may be suggested by a decreased  $\text{VO}_2\text{max}$ , early AT, ventilatory efficiency and decreased  $\text{PETCO}_2$ 's



## Methods

A detailed description of methods utilized in the BWH Advanced Cardiopulmonary Exercise Testing Facility has recently been published [86].

iCPET (Fig. 11.8) is best performed using a cycle ergometer to minimize upper body motion and a continuous ramp protocol to ensure a linear increment in work rate and resulting  $\text{VO}_2$ . Upright positioning most closely mimics normal physical activity but either upright or supine exercise can be utilized to derive Ppa–flow relationships [87]. Radial arterial line placement allows precise systemic blood pressure measurement, as well as serial arterial blood gases, to assess important indicators of pulmonary vascular function, including dead space volume/tidal volume, alveolar–arterial gradient and direct Fick cardiac outputs when coupled with assessment of oxygen uptake and mixed venous saturation.

We use an ultrasound-guided internal jugular approach to PAC placement so cycling exercise is unimpeded. The optimal zero reference point for central pressures (approximating the right atrium) has recently been reviewed for supine RHC [88]. It has been suggested that in the upright position mid right atrial ZRP is well approximated by the fourth intercostal space at the junction with the sternum and is used by our laboratory. Pulmonary capillary wedge pressure (PCWP) should be verified



**Fig. 11.8** iCPET setup at BWH. Non invasive CPET with breath-by breath measurement of pulmonary gas exchange and ventilation is combined with simultaneous radial and pulmonary arterial blood gas and pH sampling every minute at rest and incremental maximum exercise

based on characteristic waveforms, systemic oxygen saturation, and/or appearance on fluoroscopy. The critical extravascular closure pressure imposed by the lung parenchyma that contains the pulmonary vasculature is typically below that of the PCWP during exercise [89], and therefore PCWP can be used as the downstream pressure in order to determine transpulmonary pressure gradients ( $TPG = mPAP - PCWP$ ) and pulmonary vascular resistance ( $PVR = TPG/CO$ ). Care should be taken to maintain consistent upright posture relative to the leveled transducers throughout exercise. Serial measurements of mPAP, PCWP, and CO should be performed at regular intervals (i.e., every minute) during incremental exercise to characterize pressure–flow relationships.

Pleural pressure swings and their influence on pulmonary artery input and out-flow pressures and beat-to-beat stroke volume deserve special discussion. For instance, the exaggerated end expiratory pressures seen in the obese patient and in COPD do likely contribute dynamically increased right heart afterload by compression of alveolar vessels, which may in turn contribute to the patient's exertional intolerance. If, however, one assumes iCPET's clinical role is in the detection of early pulmonary vasculopathy or HFpEF, one might wish to eliminate the confounding effects of respiratory pressure swings. The classic approach to the problem was to ignore it and take a mean PAP or PCWP through the respiratory cycle. In the 1980s, end-expiratory measures came into vogue, largely in the mechanically ventilated patient, when it was assumed zero airway flow at end expiration would result in the least contamination of PAC derived pressures and this has recently been recommended for supine, resting RHC [90] and utilized during exercise [91, 92].

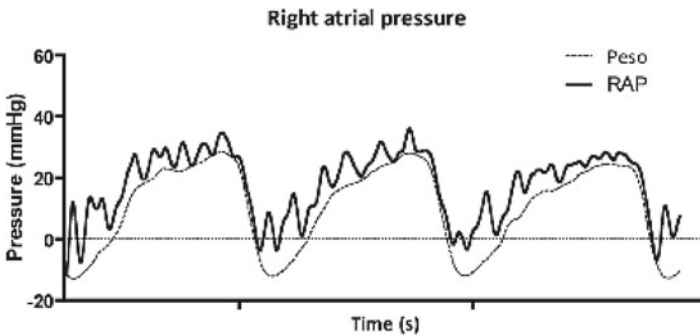
When measuring hemodynamics during exercise in COPD, subtracting esophageal pressure ( $P_{es}$ ), in order to acquire the true intra-cavitary and thereby deriving

actual transmural pressure which is critical in the detection of pulmonary vascular disease, is preferable [93]. The usefulness of the RAP waveform to estimate the pressure surrounding the heart was shown by Tyberg et al. [94]. This method assumes that pressure in the very compliant right atrium is predominantly dependent on pressure surrounding the heart (pericardial pressure, or in our case ITP), rather than by right atrial volume. We showed that this method was useful during exercise in COPD-patients, as long as the lowest point of the RAP during expiration was used. This is explained by the fact that during the right atrial contraction dissociation between RAP and ITP is created. Therefore, only the pressure of an empty and relaxing right atrium is useful to estimate ITP. We found a small bias with mPAPtm and PCWPtm when RAPnadir was used to correct expiratory mPAP and PCWP, with a very reasonable 95 % CI. This method may not be useful in patients with more pronounced right heart failure, as this causes RAP to rise, even during relaxation.

We have recently examined the worst case scenario: moderate to severe COPD referred for evaluation of suspected PH with exercise [95]. Central hemodynamics were measured simultaneously with esophageal pressure during exercise in 30 COPD patients. mPAP and PCWP were assessed in four different manners:

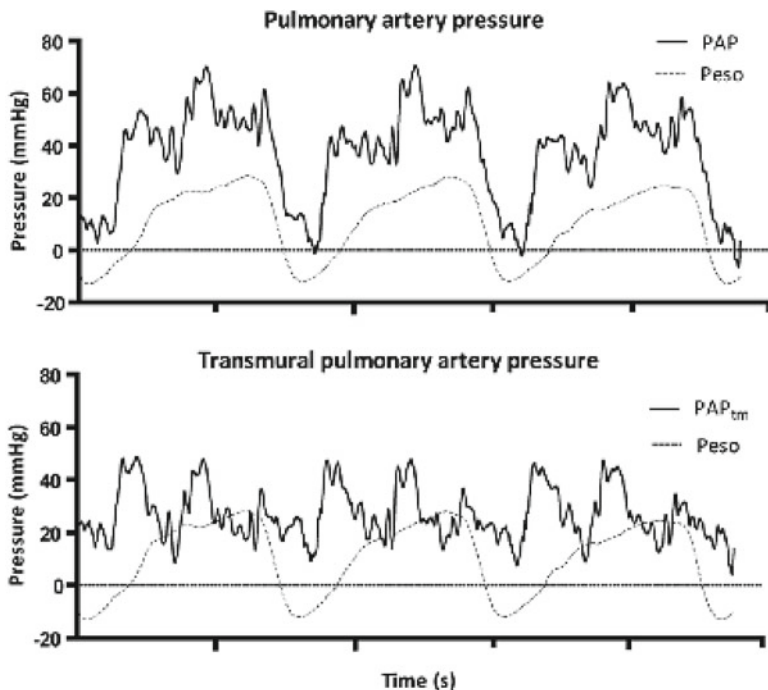
1. At end-expiration.
2. Averaged over the respiratory cycle.
3. Corrected from the right atrial pressure (RAP) nadir.
4. Corrected from the RAP respiratory swing and compared with the “gold standard” transmural mPAP and PCWP.

An example of a severe COPD patient’s PAP’s during exercise with and without correction for ITP is shown in Fig. 11.9. Maximum exercise cardiac output was  $10.9 \pm 3.8$  L/min. The large swings in Peso were transduced into all central pressure; on average responsible for a difference between inspiratory values and expiratory values of about 20 mmHg. The expiratory Peso at maximal exercise ranged from +3 to +25 mmHg. The mPAP/Q slope decreased from  $6.4 \pm 3.7$ – $4.4 \pm 3.2$  mmHg/L



**Fig. 11.9** Simultaneous measurement of RAP and esophageal pressure (Peso) at maximal exercise in the same patient as shown in Fig. 11.1. RAPnadir is the lowest point in RAP during expiration, which represents RAP during relaxation. Note that RAP falls towards Peso during relaxation. RAPswing was determined as the difference between inspiratory RAP and expiratory RAP [95]



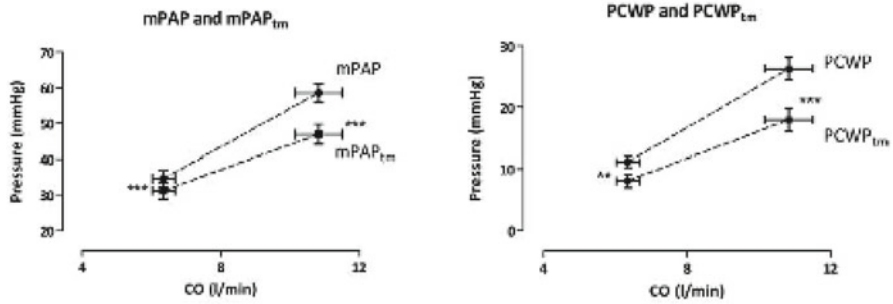


**Fig. 11.10** Example of pulmonary artery pressure before (PAP) and after (PAP<sub>tm</sub>) continuous correction for esophageal pressure (Peso) at maximal exercise in a patient with severe COPD (FEV<sub>1</sub>: 30 % of predicted) [95]

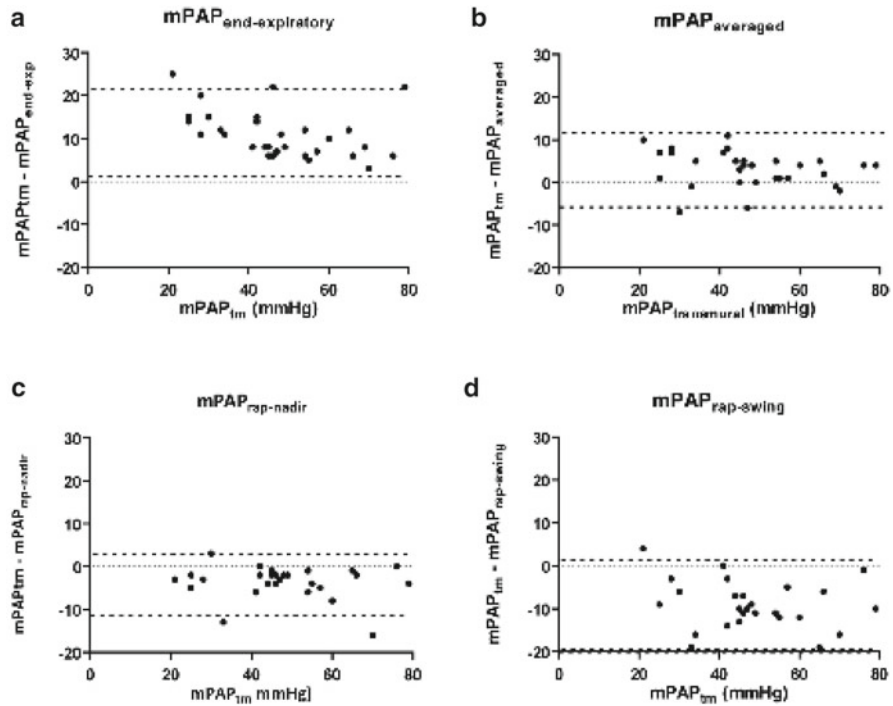
( $p < 0.001$ ) after correction for ITP. Seven patients had a mPAP/Q slope  $> 3$  mmHg before correction which decreased to  $< 3$  mmHg after correction for the ITP. Twenty-two patients had a PCWP recording. Nineteen patients of the 22 had a PCWP  $> 20$  mmHg with exercise without correction for ITP. Seven patients had a PCPW<sub>tm</sub>  $> 20$ ; in three of them PCPW<sub>tm</sub> was between 20 and 25 mmHg.

“Gold standard” mPAP<sub>tm</sub> and PCWP<sub>tm</sub> at maximum exercise were  $47 \pm 15$  and  $17 \pm 8$  mmHg respectively (Fig. 11.10). The average mPAP values at maximal exercise of the four methods were; mPAP<sub>end-exp</sub>:  $59 \pm 14$ , mPAP<sub>averaged</sub>:  $50 \pm 14$ , mPAP<sub>rap-nadir</sub>:  $44 \pm 15$ , and mPAP<sub>rap-swing</sub>:  $38 \pm 15$  mmHg. The average PCWP values at maximum exercise of the four methods were; PCWP<sub>end-exp</sub>:  $27 \pm 9$ , PCWP<sub>averaged</sub>:  $20 \pm 8$ , PCWP<sub>rap-nadir</sub>:  $15 \pm 7$ , and PCWP<sub>swing</sub>:  $11 \pm 8$  mmHg.

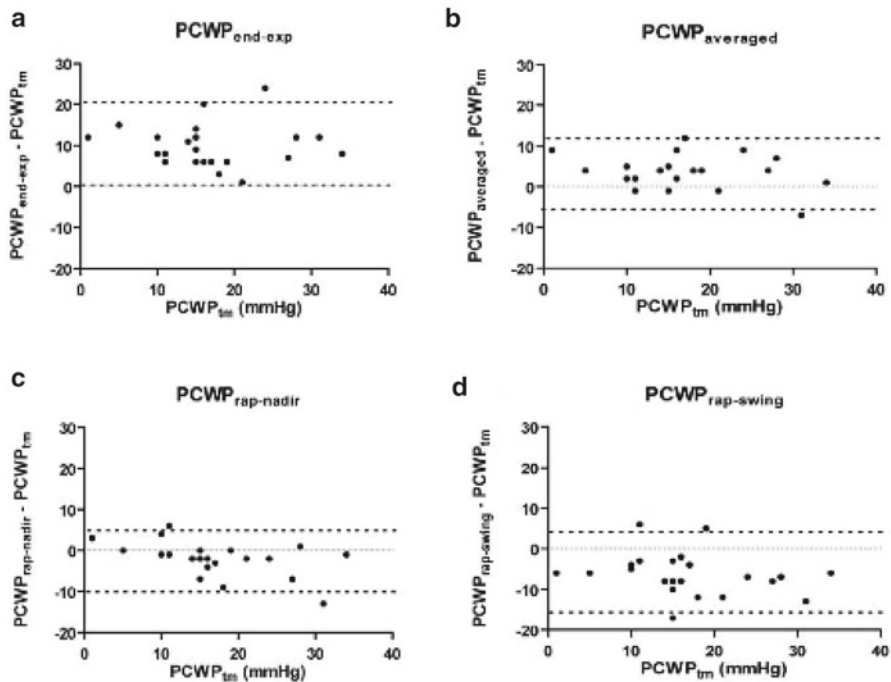
Bland-Altman analyses showed the best agreement of mPAP (Fig. 11.11) averaged over the respiratory cycle (bias: 2.5 mmHg, limits-of-agreement (-6.0 to 11.8)) and when corrected with the nadir of RAP (bias: -3.6 mmHg, limits: -11.2 to 3.9). Measuring mPAP at end-expiration (bias: 10.3 mmHg, limits: 0.5–20.3) and mPAP corrected with the RAP-swing (bias: -9.3 mmHg, limits: -19.8 to 2.1) resulted in lower levels of agreement (Fig. 11.12). Bland-Altman plots of the four methods of PCWP measurements during exercise were similar and are shown in Fig. 11.13; both are summarized in Table 11.2.



**Fig. 11.11** Average pressure flow relations before and after correction for esophageal pressure. *mPAP* mean pulmonary artery pressure, *mPAP<sub>tm</sub>* transmural mPAP (calculated as mPAP-Peso), *PCWP* pulmonary capillary wedge pressure, *PCWP<sub>tm</sub>* transmural PCWP (calculated as PCWP-Peso). \*\* $p < 0.01$ , \*\*\* $p > 0.001$  [95]



**Fig. 11.12** Bland-Altman analyses of the difference between pulmonary artery pressure (mPAP) and transmural mean pulmonary artery pressure (mPAP<sub>tm</sub>) plotted vs. the mPAP<sub>tm</sub>. (a) mPAP measured at end expiration, (b) mPAP averaged over the respiratory cycle (c) mPAP corrected with the lowest point of RAP during expiration (RAP-nadir) and (d) mPAP corrected with the swing in RAP (RAP-swing). Dotted lines represent the 95 % coincidence intervals [95]



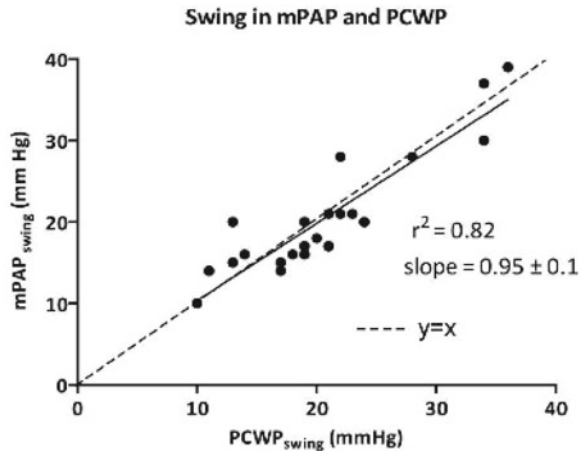
**Fig. 11.13** Bland-Altman analyses of the difference between pulmonary capillary wedge pressure (PCWP) and transmural pulmonary capillary wedge pressure (PCWP<sub>tm</sub>) plotted vs. the PCWP<sub>tm</sub>. (a) PCWP measured at end expiration, (b) PCWP averaged over the respiratory cycle (c) PCWP corrected with the lowest point of RAP during expiration (RAP-nadir) and (d) PCWP corrected with the swing in RAP (RAP-swing). Dotted lines represent the 95 % coincidence intervals [95]

**Table 11.2** Effect of ITP swings on PCWP, mPAP, and RAP {Boerrigter [95] #1813}

95 % limits of agreement (mmHg)					
	Number	r <sup>2</sup>	Bias ±SD (mmHg)	From	To
mPAP <sub>end expiratory</sub>	30	0.86	10.3 ± 5.9	0.5	20.3
mPAP <sub>averaged</sub>	30	0.92	2.5 ± 4.4	-6.0	11.8
mPAP <sub>rap_nadir</sub>	30	0.94	-3.6 ± 3.8	-11.2	3.9
mPAP <sub>rap_swing</sub>	30	0.86	-9.3 ± 5.9	-19.8	2.1
PCWP <sub>end expiratory</sub>	22	0.69	9.9 ± 5.3	-0.5	20.3
PCWPAVERAGED	22	0.75	3.2 ± 4.4	-5.3	11.8
PCWP <sub>rap_nadir</sub>	22	0.73	-2.0 ± 4.2	-2.0	4.2
PCWP <sub>rap_swing</sub>	22	0.64	-6.3 ± 5.3	-16.6	4.0

Our findings support the use of mPAP and PCWP averaged over 2–3 respiratory cycles in order to acquire more accurate assessment of the transmural values of mPAP and PCWP during exercise in COPD-patients. The patients in the present study showed a wide range of expiratory Pes<sub>o</sub> at exercise, reaching to as high as

**Fig. 11.14** Illustrates the relation between mPAP<sub>swing</sub> and PCWP<sub>swing</sub>. The swing in mPAP and PCWP did not differ (mean difference 0.9 mmHg,  $p=0.35$ ). There was a strict relation between RAP<sub>swing</sub> and PCWP<sub>swing</sub> ( $r^2=0.9$ ,  $p<0.001$ ) with a slope 1.02 and no significant difference between RAP<sub>swing</sub> and PCWP<sub>swing</sub> (mean difference 0.7 mmHg,  $p=0.28$ ) [95]

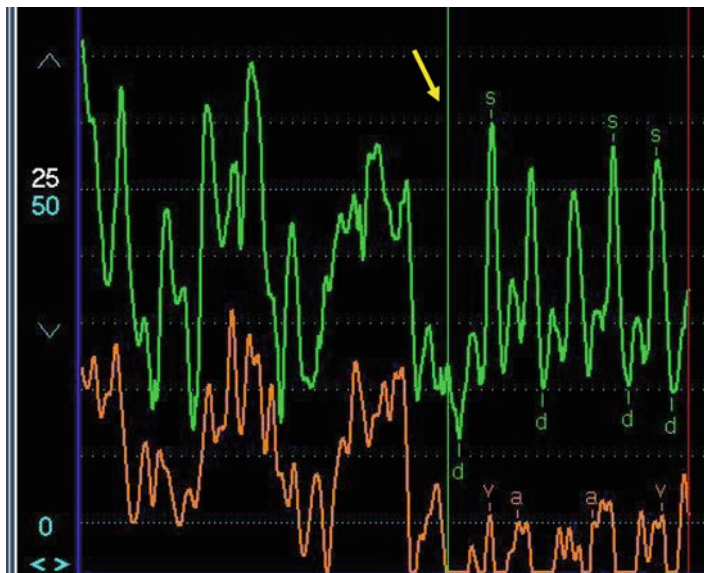


25 mmHg, which is consistent with previous studies on pulmonary mechanics. In these studies, as well as the present study, the positive excursion of *Peso* during expiration is at least as large as the negative excursion during inspiration. It is therefore not surprising that mPAP averaged over the respiratory cycle is a more realistic measure of intravascular pressure. Albeit more accurate than mPAP<sub>end-exp</sub>, mPAP<sub>averaged</sub> was still a slight overestimation, which can be explained by the increased expiratory time.

Lastly, we showed that the swings in mPAP, PCWP and RAP were similar ( $r^2=0.82$ , slope:  $0.95 \pm 0.1$ ) (Fig. 11.14). This has several convenient implications. The consequence of an identical effect of ITP swing on mPAP and PCWP is that the difference between the two, the transpulmonary pressure gradient is unaffected by the swing in ITP. This only holds when both the mPAP and PCWP being recorded at the same time point in the respiratory cycle. So, although individually, mPAP and PCWP are overestimations of intravascular pressure, the mPAP<sub>end-expand</sub> PCWP<sub>end-expand</sub> combined lead to the correct transpulmonary pressure gradient or PVR (transpulmonary gradient/CO). It underscores the importance of PVR as part of the suggested definition of exercise induced pulmonary arterial hypertension [7], as it prevents patients being diagnosed simply because of an increased ITP.

The similar effect of ITP swings in RAP and PCWP also has a potential implication in evaluating exercise hemodynamics. The increase in PCWP calculated as a ratio to the increase in RAP ( $\Delta\text{PCWP}/\Delta\text{RAP}$ ), as previously suggested [25, 96], is unaffected by ITP swings. This ratio might therefore be of potential help in the difficult situation of a high PCWP with exercise in the presence of ITP- swings. This would be especially helpful in diagnosing exercise-induced HFpEF [97].

We conclude central hemodynamics measured at end-expiration leads to an overestimation of intravascular pressures in exercising COPD-patients. More reliable data are generated by averaging pressures over the respiratory cycle or using the RAP waveform to correct for intrathoracic pressure. Assessment of the pulmonary gradient is unaffected by respiratory swings. The patients in the study of Boerrigter et al. had at least moderate airflow limitation, likely a worst-case scenario for the



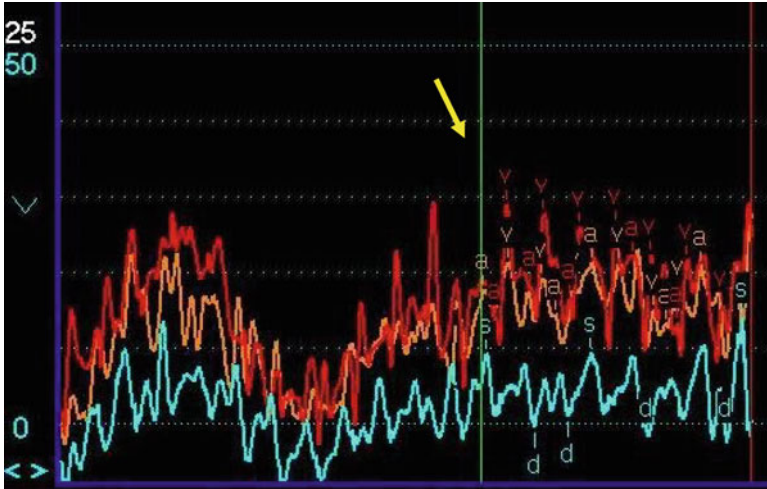
**Fig. 11.15** Effects of relaxed exhalation to FRC on PAP's during moderate exercise

influence of ITP on central pressure measurements. We can only speculate to what extent our findings can be extrapolated to patients with less severe airflow limitation such as PH. Pulmonary vascular pressure therefore should be averaged over 2–3 respiratory cycles not only in COPD [7, 8, 28] but also healthy subjects [98, 99]. Whether an averaged mPAP is a more accurate estimate of the intravascular pressure at maximal exercise in PH without parenchymal lung disease remains unknown and depends on the amplitude and the length of the inspiratory and expiratory excursions in ITP.

We have recently adopted a slow-breathing maneuver to avoid respirophasic change in pulmonary vascular pressures. Fig. 11.15 shows respirophasic change of PAP during moderate exercise; at the arrow, the patient is asked to “relax and miss a breath or two”. Over 90 % of our patients coached in this manner, with a brief practice while at rest on cycle ergometer, can successfully perform the maneuver. The same maneuver results in a stable PCWP measurement (Fig. 11.16).

### *iCPET Variables*

In a manner similar to niCPET, certain variables (Table 11.3) obtained by niCPET plus radial or arterial catheter pressure and blood gas measurements help confirm the presence of PH and differentiate PH with a TPG vs Group 2 without (pulmonary arterial vs. venous hypertension).



**Fig. 11.16** Effects of relaxed exhalation to indicate that the red tracing is the PCWP

**Table 11.3** iCPET characteristics of PH

Decreased $VO_2$ max
Decreased AT
$Qt < 80\%$ predicted
Blunted VD/VT fall $> 0.30$
Arterial $O_2$ desaturation or widened P(A-a)
$O_2 > 30$ mmHg
PAP $> 30$ mmHg
PVR $> 120$ dyn s $cm^{-5}$
PCWP/RAP slope $< 1.4$
mPAP vs. Qt slope $> 3.0$

### Cardiac Output (Qt)

The Fick Principle and conservation of mass dictate that in the steady-state,  $VO_2 = Qt \times (CaO_2 - CvO_2)$  where  $Qt$  = cardiac output and  $(CaO_2 - CvO_2)$  is the difference in  $O_2$  content (ml/L) between arterial and mixed venous blood. Thus during iCPET continuous breath-by-breath measurement of  $VO_2$  and simultaneous blood gas sampling from the distal PA port and radial artery catheter every minute allow the calculation of a Direct Fick cardiac output. Dividing predicted absolute  $VO_2$ max (ml/min) for a given patient by an expected peak  $(Ca - vO_2)$  (ml/L) =  $[Hb] \times 10$  yields an estimated  $Qt_{max}$  predicted.

Cardiac output generally limits  $VO_2$ max in healthy adults. Maximal cardiac output, which facilitates transport of oxygen from the alveolus to skeletal muscle, determines the maximal oxygen uptake and aerobic capacity to a large degree. Maintenance of  $CaO_2$  and depression of  $CvO_2$  during exercise are also circulatory

functions, requiring exquisite matching of blood flow to ventilation and tissue metabolism, respectively. Cardiac output normally increases by approximately 5 mL/min for every 1 mL/min increase in  $\text{VO}_2$  [100]. This slope is not altered by training, but maximum cardiac output improves with conditioning to four to five times resting values (up to levels of approximately 25 L/min in a young healthy individual). Maximum cardiac outputs above 40 L/min have been reported in elite athletes, and elite athletes may exhaust their breathing reserve before attaining maximal cardiac output [101].

Stroke volume (SV) increases in a hyperbolic fashion vs.  $\text{VO}_2$ , and maximum values can be augmented by up to 50 % with training [100, 102, 103]. The rise in SV during exercise is mediated in part by increased contractility, reflected by a 0.10 increase in left ventricular ejection fraction (LVEF) from rest to peak exercise [104]. Left ventricular end-diastolic volume (LVEDV) also increases by 20–40 %, augmenting SV by the Frank-Starling mechanism [105]. LV filling is enhanced during exercise by capacitance venoconstriction, greater negative intrathoracic pressures, and the pumping action of exercising limbs [106]. In a heart with normal lusitropic properties, LV end-diastolic pressure increases to approximately 20 mmHg at maximum exercise [87]. In PH, variable contributions of increased right heart afterload and decreased contractility blunt  $\text{Q}_{\text{tmax}}$  and, in turn,  $\text{VO}_{2\text{max}}$  [7].

### ***Pulmonary Artery Pressure***

Pulmonary arterial pressure responses to exercise were first characterized over 60 years ago [82]. Pulmonary hypertension was previously defined in United States and European guidelines as a mean PAP (mPAP) >25 mmHg at rest or >30 mmHg during exercise [107, 108]. In 2008, the Working Group on Diagnosis and Assessment of Pulmonary Arterial Hypertension from the Fourth World Symposium on PH (Dana Point, CA) concluded that mPAP >30 mmHg should be abandoned as a diagnostic criteria for PH whose decision has remained controversial [8, 9, 109, 110]. This decision was based on the age-dependent nature of exercise mPAP and limited data on normal subjects derived from heterogeneous levels, types, and postures during exercise testing [111]. The key paper was a meta-analysis of 47 studies describing 72 populations of healthy volunteers who underwent RHC with invasive measurement of mPAP at rest and during exercise [112]. Data were stratified by gender, age, type of exercise (i.e., cycle ergometry, treadmill exercise), body position (upright vs supine), and exercise levels (slight, submaximal, and maximal). For all subjects at maximal exercise, the ULN was 37 (supine) and 35 mmHg (upright). However, during supine exercise Ppa was significantly higher in subjects aged >50 years (29.4 + 8.4 mmHg) compared to those aged 30–50 years (20.0 + 4.7 mmHg) and 30 years (18.2 + 5.1 mmHg). The upper limit of normal for mPAP in subjects aged <50 years was 29.0 mmHg vs. 46.2 mmHg in subjects aged >50 years. Of note this analysis included TM exercise which is associated with mPAP 8–13 % higher than cycle ergometry and did not report how respiratory pressure swings were controlled for. Moreover, the PCWP and upper limit of PVR were not analyzed.

## ***Pulmonary Vascular Resistance***

In the normal human increases in cardiac output exceed the increase in TPG and PVR falls. The PVR fall during exercise is a consequence of both passive distention of a compliant circulation and active vasodilation mediated in part by NO [113]. Pulmonary capillary wedge pressure increases about 1.4 mmHg for every 1.0 mmHg increase in right atrial pressure, suggesting interdependence of right and left ventricular filling [7, 96].

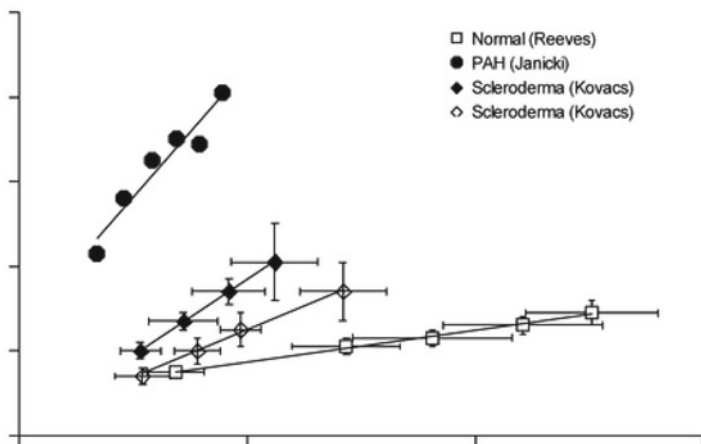
The upper limit for PVR<sub>max</sub> in healthy humans remains poorly defined. Reeves et al. [87] calculated that in young, healthy subjects, the upper limit of a normal PVR<sub>max</sub> is 56 dyn s cm<sup>-5</sup> (0.7 Wood units). Granath et al. [98] studied 27 healthy, older men (aged 71+6 years) and found an upper 95 % confidence interval for PVR<sub>max</sub> of 120 dyn s cm<sup>-5</sup> (1.5 Wood units). Kovacs et al. recently described the changes in PVR in healthy individuals primarily during supine exercise. The data were stratified by sex, age, type of exercise (i.e., cycle ergometry and treadmill exercise), body position (upright vs. supine), and exercise level (slight, submaximum and maximum). The authors concluded that a decline in PVR is seen during the exercise response in healthy normal subjects. A limitation of the study was the paucity of individuals aged >50 years; subjects aged 51–69 years were limited to only 13 and 4 patients in supine and upright positions, respectively. Of these, PVR was available for only 8 (47 %) subjects. Kovacs focused on changes of PVR from rest to exercise, but did not emphasize absolute exercise values. Of note for those subjects ages 51–70 who performed two levels of (supine) exercise, mPAP<sub>ex</sub> was 28.0±7.6 mmHg and PVR<sub>ex</sub> 57+27 dyn s cm<sup>-5</sup>. If one calculates an ULN for both mPAP<sub>ex</sub> is 43.4 mmHg but PVR<sub>ex</sub> is only 111 dyn s cm<sup>-5</sup>. The latter is in accord with the ULN for PVR<sub>max</sub> described by Granath et al. [98]. We suggest a dual definition of exercise PH include both an ULN of mPAP<sub>max</sub> and an ULN for PVR<sub>max</sub>. Until further studies are done in the aged population, 120 dyn s cm<sup>-5</sup> represents a reasonable ULN for PVR<sub>max</sub>.

## ***Pressure–Flow Relationships***

It has recently been suggested that patterns of change of mPAP vs. cardiac output ( $\Delta$ mPAP/ $\Delta$ Qt) during exercise may identify a pulmonary vasculopathy without maximally stressing the patient. Reeves et al. [87] performed exercise measurements in 63 healthy young adults at rest and at least two levels of exercise and determined average  $\Delta$ mPAP/ $\Delta$ Qt <1 mmHg/min/L. Kovacs et al. {Kovacs, 2012 #1942} reported a normal  $\Delta$ mPAP/ $\Delta$ Qt <1.06 mmHg/min/L. Our 16 normals showed a  $\Delta$ Ppa/ $\Delta$ Qt of 1.4 [7].  $\Delta$ mPAP/ $\Delta$ Qt increases as a function of age with an ULN of about 3.0 [9].

A steep  $\Delta$ mPAP/ $\Delta$ Qt relation is seen in Groups 1 and 2 PH. Fig. 11.17 shows  $\Delta$ mPAP/ $\Delta$ Qt in scleroderma, PAH compared to the normal.





**Fig. 11.17** Normal subjects (*open square*), patients with scleroderma with resting mPAP in the lower normal range (*open diamond*) and upper normal range (*filled diamond*), and patients with resting PAH (*filled circle*) demonstrate approximately linear pressure–flow responses during exercise

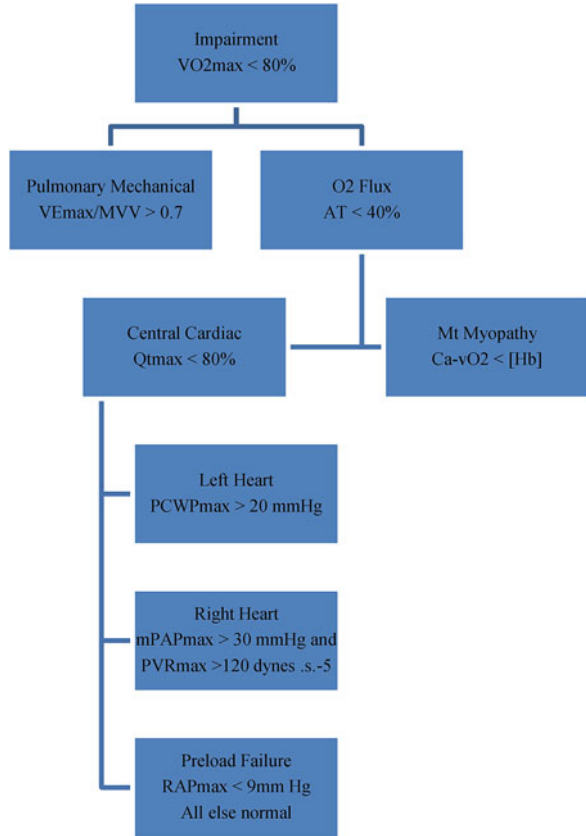
It can be concluded that the compliant pulmonary vasculature can accommodate large increases in blood flow during exercise with a proportionate modest increment in mPAP and a fall in PVR. When assessing mPAP, it is critical to account for Qt augmentation; therefore, determination of  $\Delta\text{mPAP}/\Delta\text{Qt}$  or PVR is preferable to mPAP alone.

### *iCPET Diagnostic Algorithms*

Once a central cardiac limit is established based on a low  $\text{VO}_2\text{max}$ , early AT, and a depressed  $\text{Qtmax}$ , left heart disease can be differentiated from the right using PAC-derived hemodynamics. This allows a direct Fick cardiac output ( $\text{VO}_2 = \text{Qt} \times (\text{CaO}_2 - \text{CvO}_2)$ ) and one can determine whether  $\text{VO}_2\text{max}$  is decreased because of a blunted peak cardiac output (a true cardiac limit) or failure to systemically extract  $\text{O}_2$  (e.g., a Mt myopathy). *iCPET* can be used as an initial test where PH is strongly suspected, when resting RHC numbers are borderline or when the noninvasive test is either suggestive of PH or unrevealing in a symptomatic patient. It is useful to differentiate a pulmonary mechanical from a pulmonary vascular limit in a patient with suspected Group 3 PH [64].

Patients with exercise-induced PAH, which is discussed further below, have normal cardiopulmonary hemodynamics at rest, but on *iCPET* demonstrate increased mean pulmonary artery pressure  $>30$  mmHg and pulmonary vascular resistance  $>80$ – $120$  dyn s  $\text{cm}^5$  [7, 96, 98]. In patients with normal biventricular function, an increased mean PCWP  $>20$  mmHg [96] at peak exercise in the absence

**Fig. 11.18** iCPET diagnostic algorithm



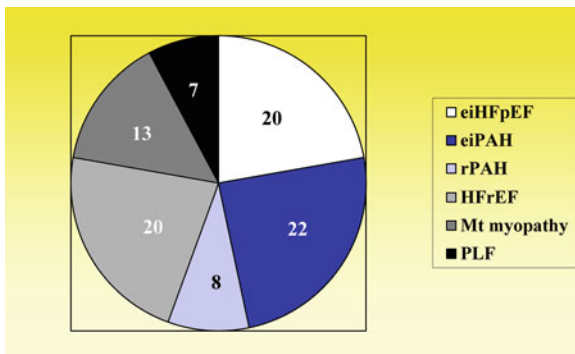
of elevations to pulmonary vascular resistance suggests exercise-induced HFpEF. Exertional intolerance may be associated with preload-dependent limitations to stroke volume and cardiac output [114]. In this patient population, failure to augment right atrial pressure on exercise is observed despite abnormally decreased cardiac output. Finally, impaired systemic O<sub>2</sub> extraction (Ca-vO<sub>2</sub> < [Hb]) indicates left to right shunting or a Mt myopathy [115].

An iCPET diagnostic algorithm is suggested Fig. 11.18. Using this approach we recently reviewed the iCPET diagnoses made at one institution over a 1-year period (Fig. 11.19).

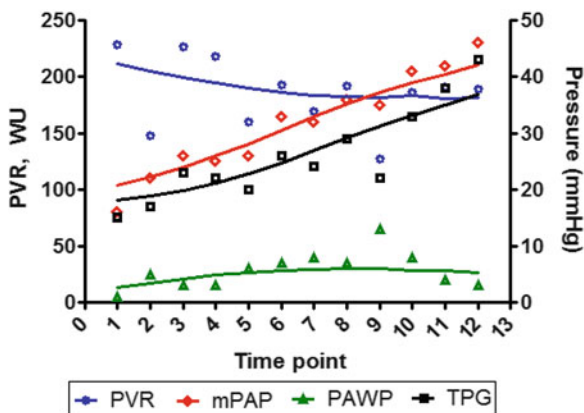
### Exercise Induced Pulmonary Arterial Hypertension (eiPAH)

Our group has studied a subset of patients with unexplained exertional intolerance, and depressed VO<sub>2</sub>max whose sole explanation is an abnormal rise in mPAP and blunted fall of PVR during incremental exercise. An example is shown in Fig. 11.20.

**Fig. 11.19** iCPET diagnoses over a 1-year period at one institution (%)

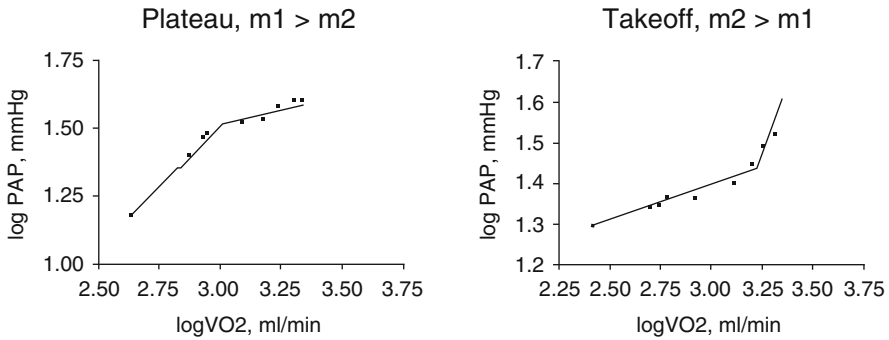


**Fig. 11.20** Central hemodynamics in representative symptomatic eiPH patient



We systematically reviewed results of 406 sequential patients undergoing iCPET to evaluate dyspnea “eiPAH” was defined as resting mPAP <25 mmHg coupled with exercise mPAP >30 mmHg, and PVR >80 dyn s cm<sup>-5</sup> and PCWP <20 mmHg [7]. Patients with eiPAH (*n*=78) were compared to patients with normal exercise capacity and hemodynamics (*n*=16) and patients with resting PAH (mPAP >25 mmHg, PCWP <15 mmHg, *n*=15). We found VO<sub>2</sub>max % predicted was lowest in resting PAH (55.8 ± 20.3 %), intermediate in eiPAH (66.5 ± 16.3 %), and highest in normals (91.7 ± 13.7 %), whereas peak mPAP (48 ± 11 vs. 37 ± 6 vs. 27 ± 4 mmHg) and PVR (294 ± 158 vs. 161 ± 60 vs. 62 ± 20 dyn s cm<sup>-5</sup>, respectively; all *P* < 0.05) followed an opposite pattern [7].

Within the eiPAH group, mPAP response to exercise followed one of two patterns. eiPAH patients with “takeoff” physiology demonstrate significantly higher VO<sub>2</sub>max and Qtmax than “plateau” eiPAH (Fig. 11.21). The “takeoff” physiology seen in the exercise induced PAH patients resemble normal/detrained “takeoff” physiology while the “plateau” physiology resembles the physiology seen in



**Fig. 11.21** *Left panel:* Representative plateau pattern of log–log plot of mPAP vs.  $\text{VO}_2$  in eiPAH. *Right:* Representative “take-off” pattern of log–log plot of mPAP vs.  $\text{VO}_2$  in eiPAH

those with resting PAH. These data suggest that eiPAH is an intermediate exercise phenotype between normal subjects and those with resting PAH and that abnormal central hemodynamics during exercise substantively contribute to exertional symptoms and impairment.

Subsequent studies have provided further evidence of the functional significance of exercise-induced elevations in PAP in “at-risk populations” for PAH [10, 116–118]. Fowler et al. [10] described 17 subjects eiPAH patients with reduced  $\text{VO}_2\text{max}$  ( $1.2 \pm 0.4$  vs.  $1.7 \pm 0.5$  L min,  $P < 0.05$ ), in turn related to decreased peak exercise cardiac output ( $72 \pm 19$  % predicted). She and her colleagues also demonstrated elevated ventilatory equivalent for carbon dioxide ( $41.0 \pm 7.3$  vs.  $31.0 \pm 2.9$ ,  $P < 0.05$ ) and reduced end-tidal carbon dioxide tension ( $32.6 \pm 3.6$  vs.  $39.4 \pm 2.7$  mmHg,  $P < 0.05$ ) at the anaerobic threshold. Kovacs et al. showed that a higher exercise mPAP and PVR in patients with “borderline” resting mPAP was associated with reduced 6-min walk distance and reduced peak workload [117].

Whyte et al. [119], examined the hemodynamic response to exercise in “at risk” patients aged  $< 50$  years with normal resting mPAP. They showed that individuals who increased mPAP  $> 30$  mmHg (24 out of 38) tended to have a higher resting mPAP and PVR. In particular, 88 % of patients with “borderline” resting mPAP of 21–24 mmHg developed mPAP  $> 30$  mmHg on mild-to-moderate exercise tended to have a lower 6-min walk test compared to the remaining 14 patients.

Whether exercise-induced elevations in mPAP and PVR provide a window into the diagnosis of early, potentially more treatable forms of PAH is uncertain [108, 120, 121]. Tolle et al. [7] described five subjects with eiPAH who underwent a repeat clinically indicated iCPET. The time to retest was  $29.8 \pm 10.7$  months. Both underlying diagnoses and treatment regimens were heterogeneous. At peak exercise, there was a nonsignificant decrease in  $\text{VO}_2\text{max}$  ( $69.8 \pm 20.2$  to  $61.2 \pm 21.9$  % predicted) that was associated with a similar change in  $\text{Qtmax}$  ( $86.4 \pm 25.6$  to  $80.0 \pm 23.8$  % predicted,  $p > 0.05$  for both), but with no change in central hemodynamics (mPAP:  $38.4 \pm 4.3$  to  $37.2 \pm 7.5$  mmHg; PVR:  $175 \pm 79$  to  $131 \pm 29$  dyn  $\text{s}/\text{cm}^5$ ,

$p > 0.05$  for both). Saggari et al. described 3/11 eiPAH SSc patients developing resting PAH over 24 weeks of open label ambrisentan [122]. Condliffe et al. found that 19 % of patients with scleroderma with eiPAH develop resting pulmonary hypertension after 2.3 years [123]. Long-term follow-up is needed, preferably as part of RCT's.

We conclude eiPAH is a clinically relevant entity whose abnormal central hemodynamics cause symptoms and substantively impair exercise tolerance. A standardized approach to its diagnosis and definition is needed. Long term prognosis, relationship to resting PH and optimal treatment need to be better defined.

### ***Exercise-Induced HFpEF***

niCPET has been used extensively in the diagnosis and management of HFpEF [124, 125] quantifying the exercise impairment and ruling out a pulmonary mechanical limit. Guazzi et al. has also shown that niCPET variables such as peak  $\text{VO}_2$ , VE/ $\text{VCO}_2$  slope, rest and peak end tidal  $\text{CO}_2$  (PET $\text{CO}_2$ ) are correlated with diastolic function in HFpEF patients [125]. Although  $\text{VO}_{2\text{max}}$  is an important prognostic factor in HFrEF, this association is not as clearly established for HFpEF patients [125].

iCPET has been used to investigate the central hemodynamics [126] and relative contributions of  $\text{Q}_t$  and systemic  $\text{O}_2$  extraction in HFpEF [97, 127, 128] iCPET has been suggested as a useful diagnostic modality in the diagnosis of eiHFpEF [129]. Borlaug et al. [97, 130] reported hemodynamic responses to exercise in 55 patients with exertional dyspnea and normal resting hemodynamic measurements. Exercise-induced changes in PCWP and PAP in patients with HFpEF were significantly higher than those in patients with noncardiac dyspnea. Kitzman et al. similarly found that compensated outpatients with HFpEF had normal resting PCWP but marked increases in exercise PCWP, suggesting that HFpEF may initially manifest with only intermittent elevations in cardiac filling pressures [130].

In HFpEF peak oxygen uptake may be additionally affected by impaired systemic  $\text{O}_2$  extraction [131, 132] as demonstrated by a reduced peak arterial-venous oxygen during iCPET.

### ***Mixed eiPH***

A significant percentage of HFpEF patients demonstrate a reactive increase in pulmonary vascular resistance (PVR) which is recognized at resting RHC, which is likely associated with worse outcome [133]. Tailored therapy of exercise-induced mixed PH, phenotyped by iCPET, shows more promise than larger clinical trials of heterogeneous, noninvasively defined HFpEF patients.

## **iCPET in Established Heart and Lung Disease**

### ***Pulmonary Arterial Hypertension***

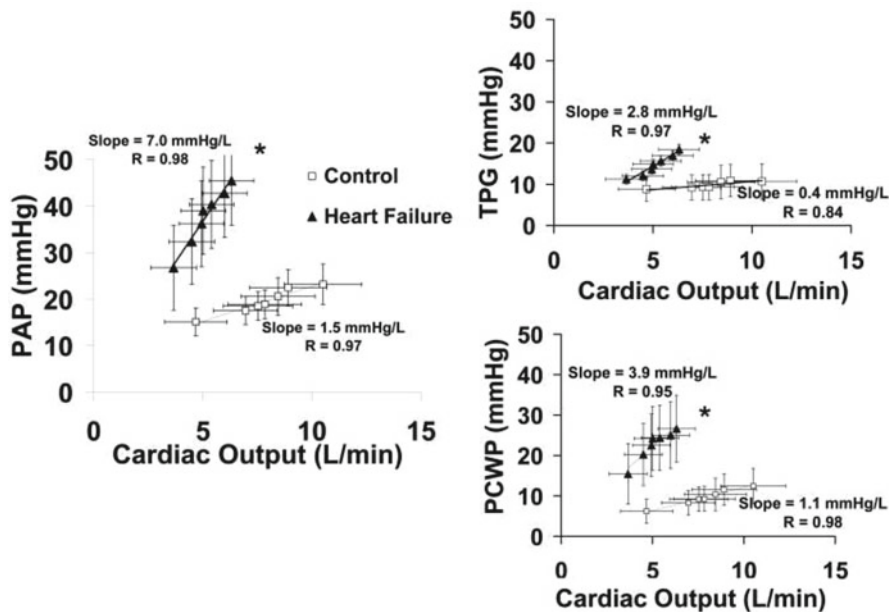
While exercise hemodynamic measurements are not necessary to confirm the diagnosis of established resting PH, they may aid in probing the compensatory capacity of the RV-pulmonary vascular unit. mPAP usually worsens during exercise when compared to rest [134]. With increased temporal resolution (e.g., q 1-min Fick Qt determinations), established PH shows a plateau in mPAP relative  $\text{VO}_2$  during maximum incremental exercise [7, 135] which may be indicative of dynamic RV dysfunction.

### ***HFrEF***

Likewise, iCPET is not necessary for the diagnosis of decompensated HF, but the pulmonary vascular response to exercise yields important mechanistic and prognostic information. For instance, Lam et al. [136] studied 60 consecutive patients with HFrEF (age  $60 \pm 12$  years, left ventricular ejection fraction  $0.31 \pm 0.07$ , mean  $\pm$  SD) and 19 controls with iCPET. During low-level exercise (30 W), LVSD subjects, compared with controls, had greater augmentation in mean PAPs ( $15 \pm 1$  vs.  $5 \pm 1$  mmHg), transpulmonary gradients ( $5 \pm 1$  vs.  $1 \pm 1$  mmHg), and effective pulmonary artery elastance ( $0.05 \pm 0.02$  vs.  $-0.03 \pm 0.01$  mmHg/mL,  $P < 0.0001$  for all). A linear increment in PAP relative to work ( $0.28 \pm 0.12$  mmHg/W) was observed in 65 % of LVSD patients, which exceeded that observed in controls ( $0.07 \pm 0.02$  mmHg/W,  $P < 0.0001$ ). Exercise capacity and survival was worse in patients with a PAP/W slope above the median than in patients with a lower slope. In the remaining 35 % of LVSD patients, exercise induced a steep initial increment in PAP ( $0.41 \pm 0.16$  mmHg/W) followed by a plateau. The plateau pattern, compared with a linear pattern, was associated with reduced  $\text{VO}_{2\text{max}}$  ( $10.6 \pm 2.6$  vs.  $13.1 \pm 4.0$  mL/kg/min,  $P = 0.005$ ), lower right ventricular stroke work index augmentation with exercise ( $5.7 \pm 3.8$  vs.  $9.7 \pm 5.0$  g/m<sup>2</sup>,  $P = 0.002$ ), and increased mortality (hazard ratio 8.1, 95 % CI 2.7–23.8,  $P < 0.001$ ). A steep increment in PAP during exercise and failure to augment PAP throughout exercise are associated with decreased exercise capacity and survival in patients with LVSD, and may therefore represent therapeutic targets (Fig. 11.22).

### ***Chronic Obstructive Pulmonary Disease***

As noted above niCPET can differentiate between a pulmonary vascular and mechanical limit to exercise. iCPET can confirm resting or eiPH in chronic obstructive pulmonary disease (COPD). Per the discussion above [95], care must be taken



**Fig. 11.22** (Left panel) Mean pulmonary arterial pressures (PAP) relative to cardiac outputs during incremental exercise in patients with LVSD. (Right panels) Transpulmonary gradient (TPG) and pulmonary capillary wedge pressure (PCWP) responses to exercise relative to cardiac output augmentation in patients with LVSD. \* $P < 0.005$  for the comparison of pressure changes in patients with LVSD with pressure changes in controls [136]

to average input and outflow pressures through several respiratory cycles and to measure mPAP and PCWP for TPG at the same point of the respiratory cycle. Exercise stroke volume appears to be limited by PH in COPD [137]. A recent study suggested a high prevalence of eiPH in COPD [92]. We have used iCPET to determine the relative contributions of cardiac output and systemic  $O_2$  extraction to the exercise limit in COPD [138, 139].

## Conclusions

Cardiopulmonary exercise testing is an important diagnostic tool in the evaluation of the patient with suspected PH. Noninvasive testing is an appropriate screening test for unexplained exertional intolerance or the patient “at risk” for PH. It can quantify the degree of impairment, and rule out a pulmonary mechanical limit to exercise. Noninvasive parameters, especially ventilatory inefficiency and  $PETCO_2$  changes with exercise, especially when used in the context of a niCPET diagnostic algorithm, show reasonable diagnostic accuracy. niCPET can confirm the diagnosis of exercise-induced PH, distinguish between pulmonary arterial and venous hypertension, and rule out confounders such as impaired systemic  $O_2$  extraction.

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