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# Accepted Manuscript

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**Exercise ventilatory parameters for the diagnosis of reactive pulmonary hypertension in patients with heart failure**

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**ABSTRACT**

**Background:** Reactive pulmonary hypertension (PH) in left heart disease is associated with poor prognosis. This study aimed to evaluate the diagnostic utility of exercise ventilatory parameters on cardiopulmonary exercise testing for the diagnosis of reactive PH in patients with heart failure (HF) and reduced ejection fraction.

**Methods:** This was a single-centre, retrospective analysis of a prospectively collected database of 131 patients with HF who underwent in-hospital assessment for heart transplantation. Pulmonary hemodynamics was assessed by direct cardiac catheterization. Minute ventilation/carbon dioxide production (VE/VCO<sub>2</sub>) slope, partial pressure of end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) changes on exercise, oxygen pulse, and exercise oscillatory ventilation were determined from cardiopulmonary exercise testing.

**Results:** Sixty-one of 131 consecutive patients had reactive PH. VE/VCO<sub>2</sub> slope (>41), change in ETCO<sub>2</sub> on exercise (<1.2mmHg) and exercise oscillatory ventilation were independently associated with reactive PH. These 3 parameters in combination produced 3 possible diagnostic scenarios: (i) if all 3 criteria ("if all") were present, (ii) if any 2 of the 3 criteria ("2 of 3") were present and (iii) if any of the criteria ("if any") were present. The corresponding positive/negative likelihood ratios for reactive PH if all 3 criteria were present were 3.73/0.83, if 2 of the 3 criteria were present were 2.19/0.45, and if any of the 3 criteria were present were 1.75/0.11. The post-test probability increased from 46% to 76% ("if all" present) and reduced to 9% (if none of the criteria present).

**Conclusion:** Ventilatory parameters on cardiopulmonary exercise test are associated with reactive PH in patients with HF. The absence of abnormalities in these 3 ventilatory parameters can effectively exclude reactive PH in patients with HF and poor ejection fraction.

**BACKGROUND**

Pulmonary hypertension (PH) is commonly associated with left ventricular dysfunction, as elevation in left-sided filling pressure results in corresponding passive increase in pulmonary arterial pressure. However, some patients develop super-added pulmonary vascular disease, which may manifest as further elevation of transpulmonary gradient (TPG) or pulmonary vascular resistance (PVR) on cardiac catheterization – so-called reactive PH<sup>1</sup>. In some cases, the severity of reactive PH and elevation in TPG and PVR may appear disproportionate to the increase in left-sided filling pressure (pulmonary artery wedge pressure of  $\leq 25$ mmHg), and this has been referred to as out-of-proportion pulmonary hypertension. An increase in mortality has been reported in patients with reactive PH and decompensated heart failure (HF)<sup>2</sup>. Reactive PH is also associated with poor outcomes from orthotopic heart transplantation, even if the abnormal pulmonary hemodynamics were reversible<sup>3</sup>. Therefore, the identification of reactive PH in left heart failure may guide prognosis and therapeutic interventions.

Cardiopulmonary exercise testing is widely used in the assessment of the severity and prognosis in patients with HF. In particular, abnormal ventilatory response on exercise, as evidenced by an increased slope of ventilation to carbon dioxide (CO<sub>2</sub>) production (VE/VCO<sub>2</sub>), oscillatory ventilation and reduced partial pressure of end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) are well described in patients with HF<sup>4,5,6</sup>. These abnormalities in ventilatory parameters in HF have been attributed to ventilation-perfusion mismatch, chemoreflex deregulation, ergoreceptor activation and reduced cardiac output<sup>7</sup>. Similar ventilatory abnormalities on cardiopulmonary exercise testing have been described in patients with pulmonary vascular disease<sup>8</sup> and patients with PH associated with left heart disease<sup>9</sup>. Despite these well reported associations between ventilatory abnormalities, heart failure and PH, cardiopulmonary exercise testing has not been systematically evaluated for the diagnosis of reactive PH in left heart disease based on invasive cardiac catheterization. Hence, this study aimed to evaluate the utility of

ventilatory parameters on cardiopulmonary exercise testing for the diagnosis of reactive PH in patients with heart failure against the current standard of direct cardiac catheterization.

## **METHODS**

### **Study Design and Patient Population**

We prospectively included consecutive ambulant patients with heart failure (New York Heart Association (NYHA) class III or IV) who underwent in-hospital assessment for heart transplantation between November 2011 and April 2013 at University Hospital Birmingham NHS Foundation Trust (Birmingham, United Kingdom). The patients completed all the assessments during their in-patient stay. Patients with congenital heart disease, acute decompensated heart failure or severe cardiogenic shock requiring inotropic support or urgent mechanical circulatory support (including intra-aortic balloon pump) were excluded from this study. Patients with significant contraindications or 'too well' for transplantation would not undergo in-hospital assessment and were not included. Baseline demographic data, including information on the medical history and current use of medications were collected from all the patients at the time of heart transplant assessment. The investigations/procedures were performed in accordance with our institution's protocol for assessment for heart transplantation and approval from the NHS Research Ethics Committee was not required.

### **Cardiopulmonary exercise test**

Each patient underwent a supervised, progressively increasing, symptom-limited cardio-pulmonary exercise testing (ramp protocol) on a treadmill. The ramp protocol was personalized to achieve a peak exercise of between 8-12 minutes. Ventilatory expired gas analysis was obtained with a metabolic cart (Powercube, Ganshorn Medizin Electronic). The oxygen and carbon dioxide sensors were calibrated before each test with gases with known oxygen, nitrogen, and carbon dioxide concentrations. The flow sensor was also calibrated before each test with a 3-L syringe. The oxygen

uptake (VO<sub>2</sub>), carbon dioxide production (VCO<sub>2</sub>), and minute ventilation (VE) were collected throughout the exercise test. PeakVO<sub>2</sub> was expressed as the highest 30-s average value obtained during the last stage of the exercise test. Oxygen pulse is derived from VO<sub>2</sub> divided by heart rate and the value at anaerobic threshold was reported as previous studies have shown that stroke volume estimation most closely approximated the directly measured stroke volume at anaerobic threshold, particularly in patients with significant heart failure<sup>10</sup>. Measurements of partial pressure of end-tidal CO<sub>2</sub> at rest (Rest ETCO<sub>2</sub>) and at anaerobic threshold (ETCO<sub>2</sub> AT) were collected as changes in end-tidal CO<sub>2</sub> during exercise has been well-reported in patients with heart failure and correlates with the severity of ventilation: perfusion mismatch<sup>11,12</sup>. Change in ETCO<sub>2</sub> (delta ETCO<sub>2</sub>) was the difference in these 2 ETCO<sub>2</sub> measurements. Ten-second averaged VE and VCO<sub>2</sub> data, from the initiation of exercise (after the warm-up period) to the point of ventilatory threshold were used to calculate the VE/VCO<sub>2</sub> slope.

Exercise oscillatory ventilation was defined in accordance with the recent consensus statement as oscillatory wave amplitude of at least 15% of resting average VE, which persisted for at least 60% of the exercise<sup>13</sup>.

#### **Transthoracic echocardiography**

Transthoracic echocardiography was performed in accordance with standard guidelines. The left ventricular end-systolic, -diastolic volumes and ejection fraction (EF) were obtained by Simpson's method from 2-dimensional apical images. The tricuspid annular plane systolic excursion (TAPSE) was measured by M-mode in the apical view as a measure of right ventricular function. Mitral and tricuspid regurgitation was quantified by Doppler in accordance with current recommendations<sup>14</sup>. Restrictive transmitral filling pattern was defined by an E/A ratio of > 2 and/or an E wave deceleration time of < 140ms<sup>15</sup>.

#### **Right heart catheterization**

Right atrial (RA), right ventricular (RV), pulmonary artery (PA) and pulmonary artery wedge pressures (PAWP) were recorded at end-expiration with a balloon-tipped catheter. Cardiac output was measured by thermodilution (using an average of three measurements agreed within 10%) with cold, refrigerated injectate (5% glucose). Transpulmonary gradient (TPG) was calculated as: mean PA – mean PAWP. Pulmonary vascular resistance (PVR) in Woods units was calculated as: TPG/cardiac output. Pulmonary artery capacitance was calculated as stroke volume/pulmonary artery pulse pressure. Right ventricular stroke work (RVSW) was calculated as: SV x (mean PA – mean RA pressure) x 0.0136.

Patients were divided into 3 groups based on their pulmonary hemodynamics: (i) no PH if mean PA pressure < 25mmHg; (ii) patients with passive PH if mean PA pressure > 25mmHg but PVR < 3WU and TPG < 12mmHg, and (iii) patients with reactive PH if mean PA pressure > 25mmHg and PVR > 3WU or TPG  $\geq$  12mmHg. These criteria were based on current recommendations and guidelines<sup>1,16</sup>.

### Statistical Analyses

Continuous variables are reported as mean  $\pm$  standard deviation (SD) or median (Interquartile range, IQR) and categorical variables as proportions. Characteristics of the 3 groups of patients (no pulmonary hypertension, passive PH and reactive PH) were compared by ANOVA (and Tukey's post hoc test) or Kruskal-Wallis for parametric and non-parametric data respectively. Multivariate analysis was performed to identify independent associations with the presence of reactive PH. The multivariate analysis included for baseline variables that were significantly different between groups (LVEF, LVESVi, TAPSE, MR, NT pro-BNP and cardiopulmonary exercise test parameters). Mitral regurgitation was added to the model due to reported association with pulmonary hypertension. Receiver operating characteristic (ROC) curve analysis was used to assess the sensitivity/specificity of the ventilatory parameters for reactive PH. Sensitivity, specificity and likelihood ratios for the combined diagnostic criteria were then calculated for the presence of reactive PH. Likelihood ratio



for a positive test (LR+) is defined as sensitivity/(1-specificity) and likelihood ratio for a negative test (LR-) is defined as (1-sensitivity)/specificity. All statistical analyses were performed using R (version 2.7.0) and a two sided p-value of <0.05 was considered statistically significant.

## RESULTS

One hundred and thirty one consecutive patients with heart failure were included in this study. Seven patients were excluded – 3 patients unable to manage exercise test (one patient was an amputee, one patient suffered from left leg weakness due to prior stroke and one patient had leg weakness due to Becker's muscular dystrophy), 4 did not reach anaerobic threshold. Sixty-one of the 131 patients had reactive PH. Of the 7 excluded patients, 2 had reactive PH. We were unable to identify AT with confidence in 12 patients – 8 in the reactive and 4 in the non-reactive PH groups. All of whom had oscillatory ventilation on exercise. In the absence of identifiable AT, we used the peak value for calculating the delta ETCO<sub>2</sub>. This is based on previous studies indicating relatively minor change in ETCO<sub>2</sub> from 50% load to peak exercise<sup>11</sup>. There were no significant differences in baseline demographics between groups. Patients with reactive PH were treated with higher doses of furosemide but there were no other statistically significant differences in conventional heart failure therapy [TABLE 1]. Patients with reactive PH had more severe right and left ventricular dysfunction, with suggestion of higher filling pressures from non-invasive tests, as evidenced by greater prevalence of restrictive transmitral filling pattern and NT pro-BNP levels.

Patients with reactive PH had greater abnormalities on cardiopulmonary exercise test [TABLE 2] and pulmonary hemodynamics [TABLE 3]. On multivariate analysis, only VE/VCO<sub>2</sub> slope ( $\beta=0.139$ ,  $p<0.001$ ), delta ETCO<sub>2</sub> ( $\beta=-0.397$ ,  $p=0.004$ ) and exercise oscillatory ventilation ( $\beta=0.269$ ,  $p=0.045$ ) were independently associated with the presence of reactive PH. Ventilatory slope ( $r=0.451$  and  $r=-0.498$ ) and delta ETCO<sub>2</sub> ( $r=-0.361$  and  $r=0.423$ ) correlated with pulmonary vascular resistance and

pulmonary capacitance, respectively (all  $p < 0.001$ ). Change in  $\text{VO}_2$  from rest to peak exercise (delta  $\text{VO}_2$ ) was correlated with PVR ( $r = -0.269$ ,  $p = 0.002$ ) and pulmonary capacitance ( $r = 0.338$ ,  $p < 0.001$ ).

On ROC analysis, the AUC for  $\text{VE}/\text{VCO}_2$  slope delta  $\text{ETCO}_2$  and exercise oscillatory ventilation were 0.79, 0.74 and 0.62; and the diagnostic threshold for  $\text{VE}/\text{VCO}_2$  slope of  $>41$  and delta  $\text{ETCO}_2$  of  $<1.2$  provided the optimal balance of sensitivity and specificity. The odds ratios threshold for  $\text{VE}/\text{VCO}_2$  slope of  $>41$ , delta  $\text{ETCO}_2 < 1.2$  and exercise oscillatory ventilation were 6.86 (95% CI: 3.1-15.0), 3.27 (95% CI: 1.58-6.75) and 2.1 (95% CI 1.01-4.62) respectively for the presence of reactive PH. These 3 parameters formed the basis for the diagnostic criteria for reactive PH.

The diagnostic value of these 3 ventilatory parameters were further analysed to determine their sensitivity, specificity and likelihood ratios. The number of patients who met the individual criteria is shown in FIGURE 1. These 3 parameters were then combined to produce 3 possible diagnostic scenarios: (i) if all 3 criteria ("if all") were present, (ii) if any 2 of the 3 criteria ("2 of 3") were present and (iii) if any of the criteria ("if any") were present. The corresponding sensitivities and specificities for reactive PH if all 3 criteria were present were 21% and 94%, if 2 of the 3 criteria were present were 69% and 69%, and if any of the 3 criteria were present were 95% and 46%. A flow diagram in line with the STARTD initiative<sup>17</sup> is shown in FIGURE 2.

As the diagnostic value of a specific test is dependent on the prevalence of the condition in a population, the likelihood ratios (LR) were also computed to determine the diagnostic value of these 3 ventilatory parameters for reactive PH based on the 46% prevalence of reactive PH in this study and also on a 50% lower prevalence of 23%. The likelihood ratios for positive and negative tests and the corresponding post-test probability of reactive PH are shown in TABLE 4. Despite the significant positive likelihood ratios, the post-test probability of these 3 criteria remained limited. In contrast, the likelihood of reactive PH is low in the absence of any of the 3 criteria in both high and low

prevalence conditions, and effectively excludes the presence of reactive PH in patients with heart failure.

We also examined the subgroup of patients with out-of-proportion PH. There were 11 patients with 'out-of-proportion' PH, characterized by TPG > 12, PVR > 3 and wedge pressure  $\leq$  25mmHg. Of these 11 patients, 7 patients had 1 of 3, 2 patients had 2 of 3 and 2 patients had all 3 criteria. Therefore, the absence of any criteria excluded 'out-of-proportion' PH, based on our analysis in this small subgroup of patients.

## DISCUSSION

This study evaluated the diagnostic utility of ventilatory parameters for reactive PH in heart failure. Three parameters were independently associated with reactive PH in this study: VE/VCO<sub>2</sub> slope, delta ETCO<sub>2</sub> and exercise oscillatory ventilation. These 3 parameters, applied in combination are associated with reactive PH in heart failure. However, our data suggest that the diagnostic utility of these ventilatory parameters lies predominantly in the exclusion of reactive PH in patients with heart failure, as the positive likelihood ratios and post-test probability were limited.

Pulmonary hypertension is a well recognized complication of left heart failure. The association between pulmonary artery pressure and prognosis is well documented in patients with heart failure<sup>18</sup>, with more recent studies demonstrating increasing risk of adverse outcome with higher pulmonary vascular resistance and transpulmonary gradient<sup>19</sup>. Similar findings have been reported in patients with decompensated heart failure<sup>2,20</sup>. In addition, reactive PH is associated with poor outcomes from orthotopic heart transplantation<sup>21</sup>. Hence, the identification of reactive PH in left heart disease may have clinically significant implications for treatment and prognosis.

Abnormalities in ventilatory parameters on cardiopulmonary exercise tests are well described in patients with PH and left heart disease. Previous studies have correlated these ventilatory abnormalities with hemodynamic changes<sup>22</sup>, pulmonary vascular disease<sup>23</sup> and clinical outcomes<sup>24,25</sup>. These observations formed the basis for further evaluation of PH in left heart disease against invasive cardiac catheterization, which is currently the accepted standard in clinical practice. Guazzi et al<sup>26</sup> evaluated the use of cardiopulmonary exercise testing for the diagnosis of PH with left heart disease. The authors reported that a raised VE/VCO<sub>2</sub> slope (>36), low peak ETCO<sub>2</sub> response (<34mmHg) and the presence of exercise oscillatory ventilation predicted elevated pulmonary artery systolic pressure estimated on echocardiography. However, although useful, there are limitations in the use of echocardiography in estimating pulmonary artery pressures<sup>27</sup>. Hence, our study extends the findings reported by Guazzi et al with direct invasive hemodynamic measurements to define reactive PH, and our findings are consistent with these earlier reports on the association between ventilatory parameters on cardiopulmonary exercise testing and PH in left heart disease. The prevalence of ventilatory abnormalities on exercise, including exercise oscillatory ventilation was high in this study. We believe this reflects the heart failure severity in our patients, who were all referred for heart transplantation. Indeed, the clinical, echocardiographic and cardiopulmonary parameters are all consistent with a population of patients with advanced heart failure.

A strong post-test probability of reactive PH with left heart disease may be intuitive in light of the well-documented association between abnormal ventilatory parameters and pulmonary vascular disease. Indeed, the positive likelihood ratios for all 3 scenarios (“if all”, “2 of 3” and “if any”) were statistically significant, which is consistent with the reported association between abnormal ventilatory parameters and pulmonary vascular disease. However, while abnormalities in all 3 ventilatory parameters would increase the pre-test probability of 46% to a post-test probability of 76%, the value of these ventilatory parameters as a “rule-in” test in clinical practice would be somewhat limited. In contrast, the negative likelihood ratio in the absence of any of these

ventilatory abnormalities may be clinically significant as a “rule-out” test, as it would reduce the pre-test probability of 46% to a post-test probability of 9%, effectively excluding reactive PH in a population of patients with severe heart failure. The diagnostic value of these ventilatory parameters remained unchanged with an assumed lower (23%) prevalence of reactive PH.

Patients with out-of-proportion PH represent a complex group. It is believed that these patients have mixed pulmonary vascular disease, which may have therapeutic implications. Based on a small number of patients with out-of-proportion PH, the absence of any of the 3 criteria appeared to exclude out-of-proportion PH in our study. These findings are preliminary and deserve further assessment.

We did not specifically study patients with heart failure and normal ejection fraction (HFnEF). Pulmonary hypertension is well described in patients with HFnEF<sup>28</sup>, which is consistent with the prevailing paradigm of elevated left-sided filling pressure as the inciting stimulus for the development of pulmonary hypertension. Similar exercise ventilatory changes, including exercise oscillatory ventilation have been described in patients with HFnEF and PH<sup>29,30</sup>, which suggests similar pathophysiological changes (eg: ventilation-perfusion mismatch, chemoreflex deregulation, ergoreceptor activation and reduced cardiac output) in patients with heart failure irrespective of the measured ejection fraction. On this basis, we speculate that exercise ventilatory parameters would have similar diagnostic value in patients with HFnEF and PH, although they have not been systematically evaluated for the detection of reactive PH in these patients.

Cardiopulmonary exercise testing has a well-established role in the assessment of heart failure. A number of exercise-derived parameters on cardiopulmonary exercise test have been described in heart failure, primarily for the assessment of prognosis<sup>31,32</sup> since the initial description of VO<sub>2</sub> in relation to heart transplantation<sup>33</sup>. Our study, building on the established association between

ventilatory abnormalities and adverse pulmonary hemodynamics, suggests that exercise ventilatory parameters may have diagnostic utility in excluding reactive PH in patients with heart failure. Our findings should not obviate the need for cardiac catheterization in patients undergoing assessment for heart transplantation as the pre-test probability is high, the consequences of transplant graft dysfunction in the face of adverse pulmonary hemodynamics are catastrophic and the risks of cardiac catheterization are low and may provide additional hemodynamic information to guide therapy and prognosis<sup>34</sup>. However, our findings may be relevant in patients with less severe heart failure and low pre-test probability in effectively excluding reactive PH. A robust non-invasive assessment modality may also guide the therapeutic interventions (and response), as investigators continue to explore potential therapy in patients with PH and left heart disease<sup>35</sup>.

#### Study limitations

This study will have the inherent limitations of a single centre observational study, consisting of patients with severe heart failure undergoing assessment for transplantation. The latter in particular, may limit external validity when applied to the wider population of patients with less severe heart failure. Examination of the diagnostic value of these criteria using a lower prevalence of reactive PH (a lower prevalence of reactive PH was assumed in patients with less severe heart failure) may mitigate, but would not abolish this limitation. Secondly, this is a relatively small study. However, we have endeavoured to characterize our patients in detail and our data should provide the basis for further evaluation and validation with a larger clinical study. In particular, mitral valve disease is associated with the development of PH, and combining echocardiographic assessment of mitral regurgitation with exercise ventilatory parameters may improve the positive likelihood ratio for reactive PH. The potential of combining multiple non-invasive modalities for the detection of reactive PH deserves further study. Finally, this study included only patients with PH in association with reduced left ventricular ejection fraction. Hence, the results may not be applicable to other forms of PH or in patients with preserved ejection fraction.

**CONCLUSION**

Ventilatory parameters on cardiopulmonary exercise test are associated with reactive PH in patients with heart failure. The positive likelihood ratios of these parameters for reactive PH were statistically significant, but clinical applicability as a “rule-in” test may be limited. In contrast, the absence of any of these ventilatory abnormalities can effectively exclude reactive PH in patients with heart failure, and be useful as a “rule-out” test.

TABLE 1: Patient characteristics

	Overall (n=131)	No PH (n=21)	Non-reactive PH (n=49)	Reactive PH (n=61)	P
Age (years)	49 ± 11	49 ± 6	49 ± 3	50 ± 3	0.860
Males (n, %)	107 (82)	76	92	75	0.067
BMI	26 ± 4	25 ± 2	27 ± 1	27 ± 1	0.319
Ischemic (n, %)	31	38	20	38	0.115
AF (n, %)	30	38	20	34	0.184
DM (n, %)	14	19	10	15	0.586
QRSd (ms)	129 ± 28	115 ± 10	129 ± 8	133 ± 8	0.035*
ICD (n, %)	44	33	43	49	0.437
CRT (n, %)	42	29	45	44	0.396
ACEi/ARB (n, %)	109 (83)	76	82	87	0.492
B blockers (n, %)	109 (83)	86	78	87	0.405
Aldos antag (n, %)	85 (65)	57	69	64	0.603
Furosemide (mg/day)	80 (80-160)	80 (40-120)	80 (40-120)	120 (80-160)	0.043
LVEF (%)	16 (10-20)	20 (15-30)	15 (10-20)	16 (10-20)	0.017*
LVESVi (ml/m <sup>2</sup> )	91 ± 25	81 ± 9	89 ± 7	97 ± 7	0.032*
TAPSE (mm)	13 (11-15)	16 (15-18)	12 (10-15)	12 (12-14)	<0.001*
RV diameter (cm)	3.7 (3.3-4.2)	3.4 (3.0-3.8)	3.7 (3.3-4.2)	3.8 (3.5-4.4)	0.085
Restrictive (n, %)	49	5	43	69	<0.001*
Severe MR (n, %)	43	29	37	53	0.091
Na (mmol/l)	137 ± 4	138 ± 2	137 ± 1	136 ± 1	0.503
eGFR (ml/min)	60 (47-80)	63 (52-88)	58 (48-79)	60 (43-74)	0.357
NT pro BNP (ng/L)	2537 (809- 5615)	1030 (535- 2360)	3205 (935- 9201)	3264 (1294- 5480)	0.011*



BMI: body mass index; AF: atrial fibrillation; DM: diabetes mellitus; QRSd: QRS duration; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; B blocker: beta-blockers; aldosterone antag: aldosterone antagonist; LVEF: left ventricular ejection fraction; LVESVi: left ventricular end-systolic volume index; TAPSE: tricuspid annular plane systolic excursion; RV: right ventricle; MR: mitral regurgitation; Na: sodium; eGFR: estimated glomerular filtration rate; NT pro BNP: N terminal pro B-natriuretic peptide

Data as mean  $\pm$  SD or median (interquartile range)

\*Significant difference in the No PH group compared to Reactive PH and Non-reactive PH groups

**TABLE 2: Cardiopulmonary exercise test**

	<b>Overall (n=131)</b>	<b>No PH (n=21)</b>	<b>Non-reactive PH (n=49)</b>	<b>Reactive PH (n=61)</b>	<b>P</b>
Peak VO <sub>2</sub> (ml/kg/min)	10.6 ± 3.4	12.5 ± 2.1	11.0 ± 0.9	9.7 ± 0.7	0.003*
Oxygen pulse (ml/beat)	7.9 ± 2.0	8.7 ± 0.7	8.4 ± 0.5	7.2 ± 0.5	<0.001*
Circ power (mmHg.ml/min)	1098 (837- 1387)	1288 (995- 1730)	1162 (872- 1365)	1068 (809- 1295)	0.044*
VEVCO <sub>2</sub> slope	41 (38-48)	36 (34-37)	40 (37-44)	46 (41-52)	<0.001**
Rest ETCO <sub>2</sub> (mmHg)	25 (23-27)	26 (25-28)	26 (24-28)	23 (21-26)	<0.001*
AT ETCO <sub>2</sub> (mmHg)	27 (23-29)	31 (28-35)	28 (25-31)	24 (21-26)	<0.001*
Delta ETCO <sub>2</sub> (mmHg)	1.2 (0.2-3.1)	4.4 (2.5-6.2)	1.5 (0.7-3.7)	0.7 (-0.3-1.7)	<0.001**
Osc vent (n, %)	35 (27)	2 (9)	12 (25)	21 (34)	0.076**

Circ power: circulatory power; ETCO<sub>2</sub>: end-tidal carbon dioxide; AT ETCO<sub>2</sub>: end-tidal carbon dioxide at anaerobic threshold; Osc vent: oscillatory ventilation

Data as mean ± SD or median (interquartile range)

\*Significant difference in the reactive PH group compared to No PH and Non-reactive PH groups

\*\*Significant difference between all 3 groups

**TABLE 3: Pulmonary hemodynamics**

	<b>Overall (n=131)</b>	<b>No PH (n=21)</b>	<b>Non-reactive PH (n=49)</b>	<b>Reactive PH (n=61)</b>	<b>P</b>
Right atrial pressure (mmHg)	14 (10-18)	8 (6-10)	15 (11-22)	15 (13-19)	<0.001*
PA systolic pressure (mmHg)	53 (40-65)	30 (26-36)	48 (40-57)	65 (55-75)	<0.001**
PA diastolic pressure (mmHg)	27 (20-33)	13 (10-16)	26 (23-31)	32 (26-36)	<0.001**
Mean PA pressure (mmHg)	37 (29-46)	30 (12-23)	35 (29-40)	46 (38-52)	<0.001**
PA wedge pressure (mmHg)	26 (20-32)	14 (10-16)	26 (20-30)	30 (25-35)	<0.001*
TPG (mmHg)	10 (7-13)	6 (5-7)	8 (7-10)	15 (12-19)	<0.001**
CO (L/min)	3.6 (3.0-4.1)	4.4 (3.6-4.9)	3.7 (3.3-4.3)	3.2 (2.8-3.7)	<0.001*
PVR (WU)	3.0 (2.1-4.1)	1.4 (1.1-1.7)	2.4 (1.9-2.7)	4.1 (3.6-5.9)	<0.001**
Pulm cap (ml/mmHg)	1.6 (1.3-2.3)	4.0 (2.5-4.5)	1.8 (1.5-2.4)	1.3 (1.0-1.5)	<0.001**
Mean BP (mmHg)	83 (75-90)	83 (71-88)	79 (72-86)	87 (79-93)	0.001†
SVR (WU)	19 (16-24)	17 (15-20)	17 (15-20)	21 (19-27)	<0.001†
PVR/SVR ratio	0.16 (0.10-0.20)	0.08 (0.07-0.10)	0.14 (0.10-0.16)	0.20 (0.17-0.26)	<0.001**

PA: pulmonary artery; TPG: transpulmonary gradient; CO: cardiac output; PVR: pulmonary vascular resistance; Pulm cap: pulmonary capacitance; BP: blood pressure; SVR: systemic vascular resistance

Data as mean ± SD or median (interquartile range)

\*Significant difference in the No PH group compared to Reactive PH and Non-reactive PH groups

\*\*Significant difference between all 3 groups

†Significant difference in the reactive PH group compared to No PH and Non-reactive PH groups

TABLE 4: Likelihood ratios at 2 levels of prevalence of reactive PH

Criteria	Prevalence (%)	Likelihood ratio (95% CI)	Post-test probability, % (95% CI)
"If all"	46	LR+ 3.73 (1.28-11.0)	76 (53-91)
		LR- 0.83 (0.72-0.96)	42 (39-46)
	23	LR+ 3.73 (1.33-10.0)	53 (28-75)
		LR- 0.83 (0.68-1.01)	20 (17-23)
"2 of 3"	46	LR+ 2.19 (1.49-3.22)	66 (56-74)
		LR- 0.45 (0.30-0.68)	28 (21-37)
	23	LR+ 2.19 (1.51-3.18)	40 (31-49)
		LR- 0.45 (0.26-0.78)	12 (7-19)
"If any"	46	LR+ 1.75 (1.40-2.19)	60 (55-66)
		LR- 0.11 (0.03-0.33)	9 (3-22)
	23	LR+ 1.75 (1.44-2.13)	34 (30-39)
		LR- 0.11 (0.02-0.53)	3 (1-14)

FIGURE 1: Number of patients who met the individual criteria

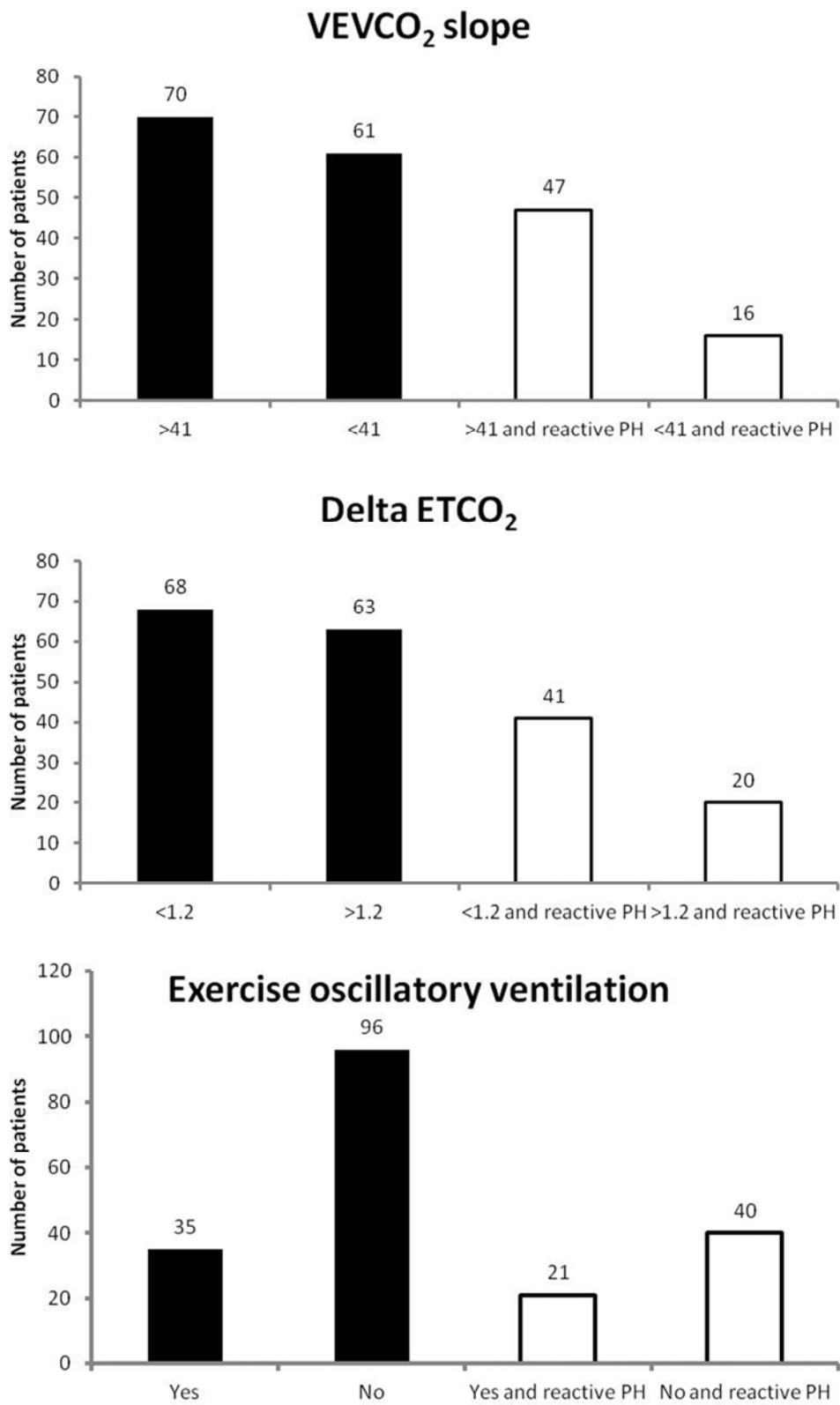
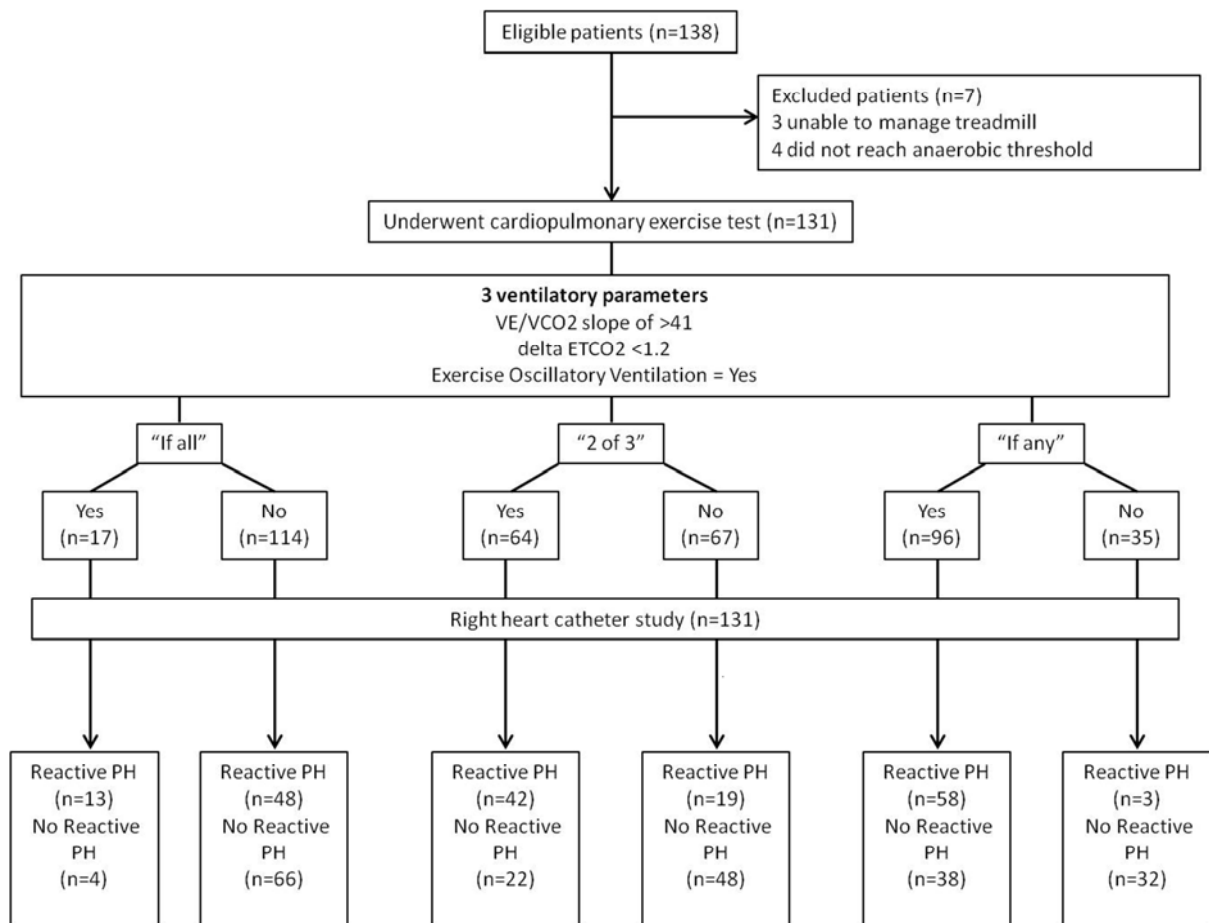


FIGURE 2: Flow diagram based on STARTD initiative.



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**Highlights****Exercise ventilatory parameters for the diagnosis of reactive pulmonary hypertension in patients with heart failure**

1. Reactive pulmonary hypertension in left heart disease (PHLHD) is common in advanced heart failure.
2.  $VE/VCO_2 > 41$ ,  $ETCO_2$  change  $< 1.2$  and oscillatory ventilation are associated with reactive PHLHD.
3. The likelihood of reactive PHLHD increased 76% if all 3 criteria were present.
4. The likelihood of reactive PHLHD reduced to 9% if none of the criteria were present.
5. Absence of these 3 ventilatory abnormalities effectively excludes reactive PHLHD in heart failure