Role of Right Ventricle and Dynamic Pulmonary Hypertension on Determining $\Delta$VO$_2$/ΔWork Rate Flattening

Insights From Cardiopulmonary Exercise Test Combined With Exercise Echocardiography

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Background—Several cardiovascular diseases are characterized by an impaired O$_2$ kinetic during exercise. The lack of a linear increase of Δoxygen consumption (VO$_2$)/ΔWork Rate (WR) relationship, as assessed by expired gas analysis, is considered an indicator of abnormal cardiovascular efficiency. We aimed at describing the frequency of $\Delta$VO$_2$/ΔWR flattening in a symptomatic population of cardiac patients, characterizing its functional profile, and testing the hypothesis that dynamic pulmonary hypertension and right ventricular contractile reserve play a major role as cardiac determinants.

Methods and Results—We studied 136 patients, with different cardiovascular diseases, referred for exertional dyspnoea. Cardiopulmonary exercise test combined with simultaneous exercise echocardiography was performed using a symptom-limited protocol. $\Delta$VO$_2$/ΔWR flattening was observed in 36 patients (group A, 26.5% of population) and was associated with a globally worse functional profile (reduced peak VO$_2$, anaerobic threshold, O$_2$ pulse, impaired VE/VCO$_2$). At univariate analysis, exercise ejection fraction, exercise mitral regurgitation, rest and exercise tricuspid annular plane systolic excursion, exercise systolic pulmonary artery pressure, and exercise cardiac output were all significantly ($P<0.05$) impaired in group A. The multivariate analysis identified exercise systolic pulmonary artery pressure (odds ratio, 1.06; confidence interval, 1.01–1.11; $P=0.01$) and exercise tricuspid annular plane systolic excursion (odds ratio, 0.88; confidence interval, 0.80–0.97; $P=0.01$) as main cardiac determinants of $\Delta$VO$_2$/ΔWR flattening; female sex was strongly associated (odds ratio, 6.10; confidence interval, 2.11–17.7; $P<0.01$).

Conclusions—In patients symptomatic for dyspnea, the occurrence of $\Delta$VO$_2$/ΔWR flattening reflects a significantly impaired functional phenotype whose main cardiac determinants are the excessive systolic pulmonary artery pressure increase and the reduced peak right ventricular longitudinal systolic function. (Circ Heart Fail. 2014;7:782-790.)

Key Words: cardiovascular diseases ■ echocardiography ■ exercise ■ hypertension, pulmonary ■ right heart failure

Cardiovascular response to exercise is primarily aimed at increasing oxygen (O$_2$) delivery to the working muscle.$^1$ Most cardiovascular diseases impair the physiology of O$_2$ uptake during exercise because of a reduction in O$_2$ delivery and an impaired extraction.$^1$

Expired gas analysis during exercise assesses the overall functional capacity and provides a series of information beyond maximal O$_2$ consumption (VO$_2$ max). Specifically, the rate of VO$_2$ increase as related to work rate ($\Delta$VO$_2$/ΔWR slope) is commonly viewed as an indicator of cardiovascular efficiency and reflects the aerobic generated ATP.$^1$ Under physiological conditions, the $\Delta$VO$_2$/ΔWR slope increases linearly with reduced variability because of the functional state.$^2$–$^4$ In the presence of a normal delivery and extraction, the $\Delta$VO$_2$/ΔWR slope mirrors the cardiac output (CO) increase during exercise. An abrupt change of $\Delta$VO$_2$/ΔWR slope (or flattening) during incremental workload, before reaching the maximum O$_2$, is commonly interpreted as the inability of the heart to adequately increase CO.$^1$ This pattern has been primarily observed in heart failure (HF) and myocardial ischemia$^5$–$^6$ but can also be observed in severe restrictive lung disease.$^7$ A reduced contractile reserve, resulting from myocardial loss and transient ischemia, limits the stroke volume (SV) increase, as well as a complete β-receptors blockade reduces heart rate (HR) reserve, both leading to blunted CO response.

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However, this abnormal $\Delta$VO$_2$/ΔWR relationship may be occasionally observed in the absence of systolic dysfunction or myocardial ischemia. The corresponding functional phenotype and pathophysiological significance are not well defined, being reasonably a marker of disease severity and risk prediction.
Conceivably, in patients with HF, the reduced contractile reserve may play a central role in the pathophysiological mechanism leading to blunted CO, but when left ventricle (LV) contractile reserve is preserved, different mechanisms must be identified.

In a recent article by Chatterjee et al., a link has been reported between the development of right ventricle–pulmonary vascular (RV-PV) uncoupling and the impaired ability to increase O₂ delivery to skeletal muscles in HF, as reflected by an impaired VO₂ kinetics during constant workload (increase in mean responsive time), intriguingly suggesting a central role of the right heart as major determinant of the functional limitation. The abnormal response of the pulmonary vascular function during exercise is also typical of patients with HF with preserved ejection fraction; furthermore, the right ventricular dysfunction is well related to functional capacity. Nonetheless, the ΔVO₂/ΔWR flattening directly reflects the abnormal functional phenotype, whatever are the underlying reasons.

According to these premises, we aimed at (1) describing the frequency of ΔVO₂/ΔWR flattening in an heterogeneous symptomatic population with cardiac disorders of different pathogenesis, characterizing its functional phenotype, and (2) testing the hypothesis that pulmonary hypertension developed during exercise (ie, dynamic), associated with reduced right ventricular contractile reserve, could be primarily responsible of the abnormal ΔVO₂/ΔWR relationship.

We performed a cardiopulmonary exercise test (CPET) combined with simultaneous exercise echocardiography looking at the cardiac and hemodynamic determinants assessed by a fully noninvasive approach.

Methods

Study Population

Consecutive patients referred to our center for functional assessment were considered for study recruitment between September 2012 and June 2013. Inclusion criteria were mild-to-severe dyspnoea during effort (New York Heart Association II to IV), capability of exercise, and adequate transthoracic acoustic windows. Of 142 eligible patients, we enrolled 136 patients (86 men, mean age 64±11 years) who fulfilled echocardiographic criteria. All patients were referred for mild-to-severe effort dyspnoea (New York Heart Association class II 58%, III 32%, and IV 10%). The underlying diseases were HF with reduced (n=54, 40%) or preserved ejection fraction (n=8, 6%), history of stable coronary artery disease (n= 18, 13%), high-risk patients with hypertrophic cardiac remodeling (n=33, 24%), hypertrophic or restrictive cardiomyopathy (n=5, 4%), and mitral or tricuspid valvular regurgitation (n=18, 13%). All patients were able to exercise, no one were on physical training. Exclusion criteria consisted of recent myocardial infarction (<3 months), unstable angina, evidence of inducible myocardial ischemia, aortic stenosis, peripheral artery disease, significant anemia (hemoglobin <10 g/dL), and respiratory diseases of at least moderate degree. All patients signed 2 informed consents, one for the execution of the test and the other for the research use of clinical and instrumental data, approved by our Local Ethical Committee. Habitual therapy was maintained during evaluation.

Cardiopulmonary Exercise Test

A symptom-limited CPET was performed on cycle ergometer for all subjects. Incremental ramp protocols were designed to obtain a standard of exercise. To facilitate simultaneous echocardiographic assessment, we limited the ramp steep to a maximum of 15 watts per minute. Ventilatory expired gas analysis was performed using a metabolic cart (Vmax; Sensormedics, Yorba Linda, CA).

Standard 12-lead ECG and blood pressure were obtained at rest, each minute during exercise, and for ≥4 minutes during the recovery phase. Baseline metabolic evaluation was performed during 1-minute rest period before exercise and during active cool-down period for ≥1 minute. Minute ventilation (VE), oxygen uptake (VO₂), and carbon dioxide output (VCO₂) were acquired breath-by-breath and averaged for 10 seconds. The V-slope method was used to determine the first ventilatory threshold (anaerobic threshold). Peak VO₂ and peak respiratory exchange ratio were expressed as the highest 10-second averaged sample obtained during the final 20 seconds.

The HR recovery at 1 minute (difference between peak HR and HR at 1 minute after the peak) and the HR at the 50% of the exercise workload were registered. O₂ pulse at peak exercise and at 1 minute of recovery was calculated as VO₂/HR.

The ΔVO₂/ΔWR slope was automatically calculated as peak VO₂—unload VO₂/T-0.75×S, where peak VO₂ is VO₂ at peak exercise, S is the slope of work rate increments in watts per minute. In patients with nonlinear ΔVO₂/ΔWR slope increasing, the overall value accounting for both slope components has been reported.

An abnormal ΔVO₂/ΔWR slope was identified when an inflection was evident in the VO₂ as a function of work rate. A significant inflection was considered when the second slope was reduced by >35% extent compared with the first one (Figure 1), with duration of ≥30 seconds, at a predicted VO₂ <85%: The beginning of the ΔVO₂/ΔWR slope inflection has been measured in the raw metabolic data set identifying, as temporal reference, the absolute workload (work at flattening) and the relative to the total exercise workload (% of total exercise at flattening).

VE/VO₂ ratio was calculated via least squares linear regression (y=mx+b, m is slope). The dead space over tidal volume (VD/VT) ratio was automatically derived using the end-tidal CO₂ (PETCO₂) to estimate the arterial CO₂ concentration according to the formula (PETCO₂—PECO₂)/PETCO₂, where PECO₂ is the CO₂ concentration in the mixed expired gas.

Exercise oscillatory ventilation (EOV) was defined as previously detailed. Briefly, criteria for EOV included the presence of ≥3 regular oscillatory fluctuations in ventilation with a minimal average amplitude of 5 L/min persisting for ≥60% of the entire exercise. In the presence of EOV, the average ΔVO₂/ΔWR slope was considered as the line of tendency among the VO₂ fluctuations. ΔVO₂/ΔWR flattening was considered if 2 different slopes were identifiable applying the previously described criteria, with the inflection point defined as the intercept between the 2 averaged slopes.

Exercise Echocardiography

We used a tiltable electronically braked cycle ergometer and standard CPET incremental ramp protocols. A Philips IE33 with a sector array of 1 to 5 MHz probe was used. A complete echocardiographic evaluation was performed at rest, recording standard projections to assess systolic, diastolic, and valvular function. Modified projections, as guidelines suggest, were used for RV and pulmonary systolic pressures measures. During exercise, the same projections were recorded every 2 minutes. When patient approached the maximal effort, monitoring the respiratory exchange ratio value of ≥1.1, we registered the same projections obtained during rest evaluation to have comparable measurements. During exercise, loop registration of ≥5 seconds was used to overcome the expected decrease of acoustic quality caused by hyperventilation. The peak state for echo recording was defined as the period from the last 30 seconds of exercise to the first minute of recovery. After that, all measurements were considered belonging to the recovery period.

One cardiologist with extensive experience on cardiovascular echocardiography performed all exercise echocardiography. All stored images were analyzed off-line after the test, in a dedicated DICOM server, by the same cardiologist. All measures were averaged at least over 3 beats in case of sinus rhythm and over 5 beats in case of atrial fibrillation. The intraobserver variability was 6% and
4%, respectively, for the main 2-dimensional and Doppler echocardiographic measures, based on a sample size of 20 subjects.

In addition, we assessed SV applying the equation $SV = VT_{LVO} \times CSA_{LVO}$, where $VT_{LVO}$ is the velocity time integral of pulsatile Doppler obtained at the level of LV outflow tract (LVOT) and $CSA_{LVO}$ is the cross sectional area of LVOT, determined using the circumference area formula. CO was obtained as $SV \times HR$, both at rest and peak of exercise.

Mitral regurgitation (MR) was assessed by qualitative measurement using a scale of 4 degrees where 1=mild, 2=mild-to-moderate, 3=moderate-to-severe, and 4= severe degree.

Systolic pulmonary artery pressure (SPAP) was estimated measuring the peak velocity ($V_{max}$) of transtricuspid continuous Doppler and calculating the gradient as $4 \times V_{max}^2$. Right atrial pressure was added to transtricuspid gradient, measuring the diameters of inferior vena cava during breathing variations. Longitudinal systolic function of RV was measured by tricuspid annular plane systolic excursion (TAPSE) from 4-chamber view.

To better study the RV-PV coupling, we considered several derived markers in addition to those directly measured. We calculated the ratio of SPAP/CO, as a marker of pulmonary pressure response normalized for CO increase during exercise, using the LV SV after assuming that no left-to-right shunt were present in our population. Therefore, we plotted the mean SPAP versus CO values, at rest and peak, identifying the different slopes in the 2 subgroups, according to the presence of $\Delta VO_2/\Delta WR$ flattening, as a marker of pulmonary pressure/flow response. We also calculated a similar ratio and slope for systemic circulation, using systolic artery pressure and CO values, to compare the pressure/flow response of both circulations. Finally, to assess the severity of the RV-PV uncoupling, we calculated the ratio of SPAP/TAPSE, both at rest and peak exercise. Conceptually, the higher the ratio, the worse the association of pulmonary hypertension and RV dysfunction.

**Statistical Methods**

Qualitative variables were summarized as percentages and quantitative as mean with SD (±SD). Parametric unpaired t test (with Satterthwaite correction for degrees of freedom) or analogous non-parametric test was used to evaluate the difference between patients with or without $\Delta VO_2/\Delta WR$ flattening. The same comparison for qualitative variables was performed by $\chi^2$ test or Fisher exact test.

To assess the independent role of pulmonary hypertension and RV response to exercise in determining $\Delta VO_2/\Delta WR$ flattening, a
Results

Population Characteristics

The \( \Delta VO_2/\Delta WR \) flattening was observed in 26.5% patients (n=36; group A) with a significantly reduced \( \Delta VO_2/\Delta WR \) slope (5.7±2.1; Table 1). Group A patients were older and prevalently women compared with group B. No differences in cardiovascular risk factors were found, whereas group A patients were more likely treated with \( \beta \)-adrenergic receptor antagonist, aldosterone antagonist, and diuretic. The distribution of the \( \Delta VO_2/\Delta WR \) flattening among different subpopulations varied as reported in Figure 2.

\[ \Delta VO_2/\Delta WR \text{ Flattening and Functional CPET Phenotype} \]

No differences were observed in LV dimensions, mass, and remodeling. Group A showed a trend toward reduced LV EF at rest and a significantly reduced EF at peak of exercise (Table 2). In group A, all CPET parameters were consonant with an unfavorable functional phenotype. As expected, these patients had a worse functional performance (lower maximal workload, peak VO\(_2\), anaerobic threshold and O\(_2\) pulse). The \( \Delta VO_2/\Delta WR \) flattening started at an averaged workload of 38±19 watts, corresponding to an averaged 53±10% of the total exercise workload. Remarkably, no \( \Delta VO_2/\Delta WR \) flattening was observed for a relative workload >65%. As to ventilatory variables, group A presented with a significantly reduced ventilatory efficiency (higher VE/VCO\(_2\) slope), lower end-tidal CO\(_2\), higher VD/VT at peak exercise, and EOV in a higher rate.

\[ \Delta VO_2/\Delta WR \text{ Flattening and Hemodynamic Phenotype} \]

No differences were observed in LV dimensions, mass, and remodeling. Group A showed a trend toward reduced LV EF at rest and a significantly reduced EF at peak of exercise (Table 3). The intrinsic LV myocardial contractility, as assessed by septal annular s wave, was the same in both groups. The prevalence of moderate-to-severe (≥3) MR at rest was similar (14% versus 14%; \( P<0.01 \)), whereas at peak of exercise group A developed a significant higher proportion of moderate-to-severe MR (39% versus 20%; \( P=0.025 \)), associated with a trend toward a bigger rest indexed left atrium volume.

Right ventricular dimensions were similar between groups. Conversely, TAPSE was significantly reduced in group A, both at rest and peak conditions (rest TAPSE: 20±5 versus 22±5 mm; \( P=0.05 \)); peak TAPSE: 22±5 versus 25±7 mm; \( P<0.01 \)).

Rest SPAP was similar between groups (rest SPAP: 37±17 versus 33±14 mmHg; \( P=ns \)); whereas a significant increase in group A at peak exercise was observed (peak SPAP: 61±19 versus 51±18 mmHg; \( P<0.01 \)). SPAP/CO was similar at rest and rounded the significance at peak.

Indexed systemic SV at rest and peak exercise were slightly, but not statistically, reduced in group A. Conversely, CO was significantly reduced at peak of exercise (7.7±2 versus 9±2.8 mL/min; \( P=0.001 \)). Similar HR at the 50% of the exercise, peak HR, and systemic pressures were found during exercise, whereas HR recovery and recovery O\(_2\) pulse were significantly reduced in group A.

To better understand the differences in terms of RV-PV coupling, we additionally considered a group B subgroup of patients (n=13) with a shallow \( \Delta VO_2/\Delta WR \) relationship (<8) but no flattening (mean slope 7.0±0.6). They had a rest and peak SPAP of 35±16 mmHg and 53±18 mmHg, a rest and
peak TAPSE of 22±6 mm and 23±6 mm, and a rest and peak SPAP/TAPSE ratio of 1.8±1.1 and 2.5±1.1, respectively.

Cardiac Determinants of ΔVO2/ΔWR Flattening
Multivariate analysis identified peak SPAP and peak TAPSE as the strongest hemodynamic cardiac determinants of the flattening, followed by rest SPAP, which did not reach a statistical significance (Table 4). The independent role of the peak SPAP and the peak TAPSE is also supported by the derived markers of RV-PV coupling, which globally resulted unfavorably modified in group A. The SPAP versus CO slope was steeper in group A describing the unfavorable pressure/flow response of pulmonary circulation, whereas no changes were observed in the systemic circulatory response (Figure 3A and 3B). Similarly, peak SPAP/TAPSE ratio was increased in group A (Figure 3C).

Overall, sex resulted the strongest predictor among all variables. Treatment with β-blockers, presence of LV systolic dysfunction or moderate-to-severe MR, and peak CO were not retained in the multivariate analysis.

According to the best model (area under the curve=0.78), for every mmHg of peak SPAP increase, the probability of ΔVO2/ΔWR flattening increased of 6%, whereas for every mm of reduced peak TAPSE, the probability increased of 12%.

Discussion
Present findings extend on the body of literature1-8 that focuses on the abnormalities in VO2 kinetics during exercise, providing an in-depth analysis on the determinants of an impaired ΔVO2/ΔWR relationship during incremental maximal exercise. To achieve this aim, the combination of CPET with simultaneous exercise echocardiography provided insightful results. Major study findings are (1) a significant rate of ΔVO2/ΔWR flattening occurrence in a heterogeneous population of symptomatic patients with different cardiovascular disorders, carrying an unfavorable functional phenotype; (2) a pathophysiological link between ΔVO2/ΔWR flattening and some degree of RV-PV uncoupling.

Relationship Between ΔVO2/ΔWR Flattening and Functional Phenotype
The ΔVO2/ΔWR flattening is a phenomenon mainly reported in patients with HF with reduced ejection fraction and in patients with extensive ischemia during exercise.5,6 This is the first study looking at the phenomenon in symptomatic patients intolerant to exercise (the majority complaining dyspnoea for moderate level of activity), irrespective of their LV systolic function. Despite patients with HF were the most represented category in our population, several others conditions presented with this abnormal response to exercise (Figure 2), and no correlation with LV EF at rest was found at the multivariate analysis. Our findings reject the exclusive link between the LV systolic dysfunction and abnormal VO2 kinetic, whereas they support the role played by the abnormal response to exercise of pulmonary pressures and right ventricular contractility.

As recently showed,8 patients with HF with reduced EF may present delayed oxygen uptake during exercise clearly exhibiting an RV-PV uncoupling, which expresses the inability of the right ventricle to augment its performance against increased exercise-induced pulmonary pressures. In their article, Chatterjee et al8 looked at a complex aspect of the oxygen kinetic during exercise, demonstrating the central role played by RV-PV in determining the functional phenotype. Using a novel, noninvasive, combined approach, in a symptomatic population with heterogeneous heart diseases, we also found a similar direct link between the functional phenotype of disrupted oxygen kinetics and an impaired RV-PV coupling. In contrast to the Chatterjee’s study,4 we looked at a qualitative, easy to recognize, phenomenon that is closely related to impaired functional capacity.

Table 2. CPET Variables According to Groups

<table>
<thead>
<tr>
<th>Group A (n=36)</th>
<th>Group B (n=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal work, watt</td>
<td>68±28</td>
<td>91±40.1</td>
</tr>
<tr>
<td>Peak VO2, mL/kg per minute</td>
<td>13.4±3.9</td>
<td>18.0±6.6</td>
</tr>
<tr>
<td>Predicted peak VO2, %</td>
<td>58±18</td>
<td>69±21</td>
</tr>
<tr>
<td>AT, mL/kg per minute</td>
<td>11.4±3.3</td>
<td>13.8±4.4</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.2±0.1</td>
<td>1.2±0.1</td>
</tr>
<tr>
<td>Peak VO2, mL/beats</td>
<td>8.2±2.3</td>
<td>10.9±3.1</td>
</tr>
<tr>
<td>Recovery VO2, mL/beats</td>
<td>7.2±2.5</td>
<td>9.2±2.5</td>
</tr>
<tr>
<td>VE/VCO2 slope</td>
<td>33.2±8</td>
<td>29.8±6.8</td>
</tr>
<tr>
<td>End-tidal CO2, mm Hg</td>
<td>32.1±4.8</td>
<td>36±5.7</td>
</tr>
<tr>
<td>HR at 50%</td>
<td>102±16</td>
<td>100±15</td>
</tr>
<tr>
<td>HRR, beats/min</td>
<td>9.5±8.7</td>
<td>14.5±10</td>
</tr>
<tr>
<td>EOV, n (%)</td>
<td>16 (44)</td>
<td>25 (25)</td>
</tr>
<tr>
<td>ΔVO2/ΔWR slope, mL/min per watt</td>
<td>5.7±2.1</td>
<td>10±2.9</td>
</tr>
<tr>
<td>Work at flattening, watt</td>
<td>38±19</td>
<td>...</td>
</tr>
<tr>
<td>Total exercise % at flattening, %</td>
<td>5±10</td>
<td>...</td>
</tr>
<tr>
<td>Rest VT/VT</td>
<td>0.30±0.07</td>
<td>0.29±0.09</td>
</tr>
<tr>
<td>% of predicted rest VT/VT</td>
<td>101.1±23.85</td>
<td>94.4±32.0</td>
</tr>
<tr>
<td>Peak VT/VT</td>
<td>0.17±0.04</td>
<td>0.15±0.05</td>
</tr>
<tr>
<td>% of predicted peak VT/VT</td>
<td>94.86±22.05</td>
<td>83.41±27.07</td>
</tr>
</tbody>
</table>

CPET results showing consistent difference across the entire functional profile (results are reported as mean±SD). ΔVO2/ΔWR indicates Δoxygen consumption/Δwork rate; AT, anaerobic threshold; CPET, cardiopulmonary exercise test; EOV exercise oscillatory ventilation; HRR@50%, HR at the 50% of the exercise; HRR heart rate recovery; RER respiratory exchange ratio; VE/VCO2 slope, ventilation over CO2 and VT/VT, dead over tidal volume.
The ΔVO₂/ΔWR flattening was definitely characterized by severely reduced peak O₂ consumption (with 1 Weber class²⁰ of difference between groups) and a significant impairment in ventilatory efficiency (also with 1 ventilatory class²¹ of difference). This was supported by an unfavorable end-tidal CO₂ and a higher prevalence of EOV. Interestingly, the ΔVO₂/ΔWR flattening occurred early (53±10% of entire exercise) suggesting an impaired O₂ kinetic response instead of the maximal VO₂ plateau. Moreover, a significant reduced HR recovery probably reflected the need for a prolonged high CO state to support the metabolic demand during recovery. All these parameters depict a potentially unfavorable outcome.

Cardiac Determinants of the ΔVO₂/ΔWR Flattening

The major novelty of the present study is that a disproportionate increase in SPAP to CO increase during exercise was the main ΔVO₂/ΔWR flattening determinant. The SPAP and the abnormal RV contractile reserve (TAPSE) resulted as the hemodynamic independent predictors of the ΔVO₂/ΔWR flattening. The different behavior of

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**Table 3. Physiological and Echocardiographic Parameters According to Groups at Rest and Peak of Exercise**

<table>
<thead>
<tr>
<th></th>
<th>Rest (n=36)</th>
<th>Peak (n=36)</th>
<th>Rest (n=100)</th>
<th>Peak (n=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume ind, mL/m²</td>
<td>67±28</td>
<td>67±24</td>
<td>67±33</td>
<td>67±33</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>LV end-systolic volume ind, mL/m²</td>
<td>39±21</td>
<td>38±22</td>
<td>34±29</td>
<td>36±28</td>
<td>0.56</td>
</tr>
<tr>
<td>LV mass ind, g/m²</td>
<td>116±42</td>
<td>...</td>
<td>109±32</td>
<td>...</td>
<td>0.36</td>
</tr>
<tr>
<td>LV RWT</td>
<td>0.36±0.07</td>
<td>...</td>
<td>0.38±0.1</td>
<td>...</td>
<td>0.36</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>47±14</td>
<td>47±17</td>
<td>52±16</td>
<td>55±17</td>
<td>0.12</td>
</tr>
<tr>
<td>Mitral S’ TDI, cm/s</td>
<td>5.9±2.3</td>
<td>7.3±2.7</td>
<td>6.3±2.0</td>
<td>7.9±3.2</td>
<td>0.35</td>
</tr>
<tr>
<td>E/A</td>
<td>1.3±0.8</td>
<td>...</td>
<td>1.3±0.9</td>
<td>...</td>
<td>0.78</td>
</tr>
<tr>
<td>Deceleration time E, ms</td>
<td>189±78</td>
<td>124±39</td>
<td>189±67</td>
<td>126±40</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>E/e’</td>
<td>20.8±11.5</td>
<td>...</td>
<td>17.6±11.9</td>
<td>...</td>
<td>0.18</td>
</tr>
<tr>
<td>Left atrium volume ind, mL/m²</td>
<td>49±25</td>
<td>...</td>
<td>42±25</td>
<td>...</td>
<td>0.16</td>
</tr>
<tr>
<td>RV end-diastolic area, cm²</td>
<td>17±5</td>
<td>16±5</td>
<td>17±5</td>
<td>17±5</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>RV fractional area, %</td>
<td>41±10</td>
<td>41±13</td>
<td>42±10</td>
<td>45±10</td>
<td>0.60</td>
</tr>
<tr>
<td>TAPSE, mm</td>
<td>20±5</td>
<td>22±5</td>
<td>22±5</td>
<td>25±6</td>
<td>0.05</td>
</tr>
<tr>
<td>SPAP, mmHg</td>
<td>37±17</td>
<td>61±19</td>
<td>33±14</td>
<td>51±18</td>
<td>0.22</td>
</tr>
<tr>
<td>LV stroke volume ind, mL/m²</td>
<td>32±9</td>
<td>36±9</td>
<td>34±11</td>
<td>39±11</td>
<td>0.52</td>
</tr>
<tr>
<td>LV CO, L/min</td>
<td>4.2±1.2</td>
<td>7.7±2</td>
<td>4.5±1.5</td>
<td>9.0±2.8</td>
<td>0.39</td>
</tr>
<tr>
<td>SPAP/CO, mmHg/L per minute</td>
<td>9.27±4.62</td>
<td>8.45±4.02</td>
<td>7.92±4.52</td>
<td>6.73±4.47</td>
<td>0.16</td>
</tr>
<tr>
<td>SPAP vs CO slope</td>
<td>8.4±5.6</td>
<td>...</td>
<td>5.9±6.2</td>
<td>...</td>
<td>0.06</td>
</tr>
<tr>
<td>SPAP/TAPSE, mmHg/mm</td>
<td>1.95±0.9</td>
<td>3.03±1.25</td>
<td>1.67±0.7</td>
<td>2.29±1.34</td>
<td>0.17</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>77±18</td>
<td>119±21</td>
<td>73±14</td>
<td>122±21</td>
<td>0.27</td>
</tr>
<tr>
<td>HR@50%</td>
<td>77±18</td>
<td>119±21</td>
<td>73±14</td>
<td>122±21</td>
<td>0.27</td>
</tr>
<tr>
<td>HR@50%</td>
<td>77±18</td>
<td>119±21</td>
<td>73±14</td>
<td>122±21</td>
<td>0.27</td>
</tr>
<tr>
<td>SAP, mmHg</td>
<td>127±15</td>
<td>156±26</td>
<td>128±18</td>
<td>169±35</td>
<td>0.81</td>
</tr>
<tr>
<td>SAP/CO, mmHg/L per minute</td>
<td>31.8±8.9</td>
<td>21.7±6.7</td>
<td>30.5±8.3</td>
<td>20.2±6.7</td>
<td>0.46</td>
</tr>
<tr>
<td>SAP vs CO slope</td>
<td>12.9±8.3</td>
<td>...</td>
<td>11.16±8.0</td>
<td>...</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean±SD. P values for unpaired t test at rest and peak are also reported. CO indicates cardiac output; E/A, early diastolic velocity/late diastolic velocity; e’, early diastolic septal velocity; EF, ejection fraction; HR@50%, HR at the 50% of the exercise; ind, indexed; LV, left ventricle; RV, right ventricle; RWT, relative wall thickness; SAP, systolic arterial pressure; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; and TDI, tissue doppler imaging.

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**Table 4. Variables Retained in the Best Regression Model for Determinants of ΔVO₂/ΔWR Flattening (AUC=0.78)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>Test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F vs M)</td>
<td>6.10</td>
<td>2.11</td>
<td>17.7</td>
<td>3.34</td>
</tr>
<tr>
<td>β-Blocker treatment</td>
<td>2.10</td>
<td>0.73</td>
<td>6.1</td>
<td>1.38</td>
</tr>
<tr>
<td>Peak MR (≥3 vs &lt;3)</td>
<td>0.31</td>
<td>0.07</td>
<td>1.42</td>
<td>−1.51</td>
</tr>
<tr>
<td>Rest SPAP</td>
<td>0.95</td>
<td>0.90</td>
<td>1.00</td>
<td>−1.75</td>
</tr>
<tr>
<td>Peak SPAP</td>
<td>1.06</td>
<td>1.01</td>
<td>1.11</td>
<td>2.56</td>
</tr>
<tr>
<td>Peak TAPSE</td>
<td>0.88</td>
<td>0.8</td>
<td>0.97</td>
<td>−2.47</td>
</tr>
</tbody>
</table>

ΔVO₂/ΔWR indicates Δoxygen consumption/Δwork rate; AUC, area under the curve; F, female; M, male; MR, mitral regurgitation; SPAP, systolic pulmonary artery pressure; and TAPSE, tricuspid annular plane systolic excursion.
SPAP and systolic artery pressure versus CO reinforces the main involvement of the pulmonary circulation (Figure 3).

These findings, altogether, strengthen the concept that when RV-PV uncoupling occurs, the $\Delta$VO$_2$/ΔWR relationship is likely to be abnormal, regardless of the underlying disorder. As sequential manifestations, a certain degree of RV-PV uncoupling first leads to a blunted increase in RV CO that, right after, induces an impaired left side CO response, unlocked by a nonlinear $\Delta$VO$_2$/ΔWR increase. Although we did not measure pulmonary vascular resistance, it is tempting to speculate that an abnormal pulmonary vasculature response occurred. An increased VE/VCO$_2$ slope and lower reduction of VD/VT both seem to point in this direction likely reflecting the occurrence of some impairment of ventilation to perfusion matching.$^{22}$

The subgroup of patients with a shallow $\Delta$VO$_2$/ΔWR slope but still preserved linear increase presented an echocardiographic profile characterized by an intermediate degree of RV-PV uncoupling between group A and B. This advances the intriguing hypothesis of a continuum between the RV-PV uncoupling and the abnormalities in the $\Delta$VO$_2$/ΔWR relationship.

The central role of the blunted SV during exercise is supported by both echocardiographic and HR data. The HR at the 50% of the exercise and peak HR were similar between groups while the peak SV showed a trend to be reduced in the group A. Considering that the $\Delta$VO$_2$/ΔWR flattening generally started at about half of the exercise, the similar HR at the 50% of the exercise and peak HR exclude an HR flattened response. Rather, a blunted SV response, during exercise and recovery, is also supported by a similar O$_2$ pulse flattening, reduced peak, and recovery O$_2$ pulse in group A (Figure 1).

Both LV systolic dysfunction and moderate-to-severe MR were not retained in the multivariate analysis. These findings discard the central role of such conditions, although a triggering role in the pathophysiological cascade cannot be excluded. As in group 2 pulmonary hypertension,$^{23}$ the increased LV filling pressure represents the trigger for developing an abnormal pulmonary vascular response. We considered the E/e’ ratio at rest, a noninvasive marker of mean LV filling pressures,$^{24}$ which showed only a trend toward higher values in group A. Invasive LV filling pressure measurement during exercise
would have provided significant insights on hemodynamic response. We did not consider the E/e' ratio during exercise because of the difficulty in correctly identifying the early diastolic velocity at elevated HR, especially in a such heterogeneous population.

As nonhemodynamic predictor at multivariate analysis, the female sex was strictly associated with ΔVO₂/ΔWR flattening. This finding can be explained by simply recognizing the sex-related difference in overall performance and CO.²⁵ It is also plausible that women might have a different pulmonary vascular response in term of vascular recruitment and desten-
tion that may better predispose to RV-PV uncoupling. Despite the potential role in reducing the CO response during exercise, β-blockers were associated with ΔVO₂/ΔWR flattening only at univariate analysis.

Limitations
The major limitation of our study is the lack of comparat-
ive invasive hemodynamic evaluation. However, we used a
prespecified strict echocardiographic protocol rejecting data
without good quality to limit potential errors, particularly for
parameters related to hemodynamic estimation, and it is likely
that our approach may result less feasible in an unselected
population because of a higher rate of inadequate acoustic
window.

We used a novel approach adapting exercise echocardiogra-
phy to CPET, differently from the long-steps protocol used in
the majority of echo laboratories. This choice has been made
to preserve the entire prognostic value of CPET, in an attempt
to optimize the clinical information deriving from both tests.
The ΔVO₂/ΔWR relationship was defined according to a
simple qualitative method with the belief that it helps to
simplify the overall information given by the ΔVO₂/ΔWR
relationship without losing its significance. However, other
nonphysiological patterns of ΔVO₂/ΔWR increase, such as
the shallow one, are worthy of further investigations, possibly
reflecting intermediate degrees of abnormal response to exer-
cise. Similarly, the patterns of ΔVO₂/ΔWR relationship are
worthy of additional validation.

Conclusions
The present study has several implications for clinical prac-
tice. First, we demonstrated the association between the
ΔVO₂/ΔWR flattening and a typical abnormal CPET pheno-
type, expanding the significance of this unfavorable marker
from a specific population of patients with HF to a heteroge-
eous population of patients symptomatic for dyspnoea and
complaining exercise intolerance.

Second, we identified the primary role of RV-PV uncou-
cpling in this abnormal functional phenotype making rea-
sionable to use the ΔVO₂/ΔWR flattening as indicator of an
abnormal pulmonary vascular response to exercise. This
finding is further reinforced by the observed association with
EOV (1.7 fold increase), a prognostic ventilatory marker of
impaired cardiopulmonary function.

Finally, although the potential prognostic value of these
findings needs to be assessed in the long term, it seems rea-
sonable to infer that such an approach could result useful in
clinical practice, given the extensive amount of functional
and hemodynamic information obtained through a comprehensive
noninvasive functional integrated approach.

Disclosures
None.

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**CLINICAL PERSPECTIVE**

Cardiopulmonary exercise test is widely used to assess functional capacity and oxygen uptake (VO$_2$). A lack of linear increase in VO$_2$ over incremental workload ($\Delta$VO$_2$/ΔWR) pattern is a sensitive indicator of impaired aerobic efficiency whose determinants are poorly investigated. An intriguing possibility to unlock underlying mechanisms and their clinical significance is combining cardiopulmonary exercise testing with exercise echocardiography. We, therefore, used this approach to explore the pathophysiology behind the $\Delta$VO$_2$/ΔWR flattening phenomenon by studying an heterogeneous population of patients symptomatic for effort dyspnoea. We found that the nonlinear $\Delta$VO$_2$/ΔWR relationship was associated with a significantly impaired functional phenotype and related cardiac determinants were exercise left ventricle ejection fraction, exercise mitral regurgitation, rest and exercise tricuspid annular plane systolic excursion, exercise systolic pulmonary artery pressure, and exercise cardiac output, but only the exercise tricuspid annular plane systolic excursion and systolic pulmonary artery pressure were retained in the multivariate analysis. This results identify the right ventricle–pulmonary vascular uncoupling as the main determinant of the abnormal $\Delta$VO$_2$/ΔWR relationship, corroborating previous studies focused on the role of pulmonary circulation. The main clinical impact of this study relies on the identification of the $\Delta$VO$_2$/ΔWR flattening abnormality as a marker of underlying right ventricle–pulmonary vascular uncoupling. Notably, the total noninvasiveness of such an integrated approach prospects further significant implications in studying specific exercise phenotypes in clinical practice.
Role of Right Ventricle and Dynamic Pulmonary Hypertension on Determining $\Delta VO_2/\Delta$ Work Rate Flattening: Insights From Cardiopulmonary Exercise Test Combined With Exercise Echocardiography

Francesco Bandera, Greta Generati, Marta Pellegrino, Valeria Donghi, Eleonora Alfonzetti, Maddalena Gaeta, Simona Villani and Marco Guazzi

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