

ORIGINAL ARTICLE

# Cardiopulmonary Exercise Testing as a Tool for Diagnosing Pulmonary Hypertension in Patients with Dilated Cardiomyopathy

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**Background:** Recently, it has become increasingly recognized that pulmonary hypertension (PH) is a particularly threatening result of left-sided heart disease. However, there have been few investigations of the impact of cardiopulmonary exercise testing (CPX) variables on PH in dilated cardiomyopathy (DCM). We evaluated the usefulness of crucial CPX variables for detecting elevated pulmonary arterial pressure (PAP) in patients with DCM.

**Methods:** Ninety subjects with DCM underwent cardiac catheterization and CPX at our hospital. Receiver operator characteristic (ROC) analysis was performed to assess the ability of CPX variables to distinguish between the presence and absence of PH.

**Results:** Overall mean values were: mean PAP (mPAP),  $18.0 \pm 9.6$  mmHg; plasma brain natriuretic peptide,  $233 \pm 295$  pg/mL; and left ventricular ejection fraction,  $30.2 \pm 11.0\%$ . Patients were allocated to one of two groups on the basis of mean PAP, namely DCM without PH [mean PAP (mPAP)  $<25$  mmHg;  $n = 75$ ] and DCM with PH (mPAP  $\geq 25$  mmHg;  $n = 15$ ). A cutoff achieved percentage of predicted peak  $\text{VO}_2$  (%PPeak  $\text{VO}_2$ ) of 52.5% was the best predictor of an mPAP  $\geq 25$  mmHg in the ROC analysis (area under curve: 0.911). In the multivariate analysis, %PPeak  $\text{VO}_2$  was the only significant independent predictor of PH (Wald 6.52, odds ratio 0.892, 95% CI 0.818–0.974;  $P = 0.011$ ).

**Conclusions:** %PPeak  $\text{VO}_2$  was strongly associated with the presence of PH in patients with DCM. Taken together, these findings indicate that CPX variables could be important for diagnosing PH in patients with DCM.

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cardiopulmonary exercise testing; dilated cardiomyopathy; peak  $\text{VO}_2$ ; pulmonary hypertension

Pulmonary hypertension (PH) occurs commonly in patients with left heart disease and is associated with increased morbidity and mortality.<sup>1,2</sup> PH associated with left heart disease is classified in group

2 of the Nice 2013 classification.<sup>2</sup> and is believed to be the most common form of PH,<sup>3</sup> with both passive and active components.<sup>1,4</sup> In patients with ischemic or nonischemic dilated cardiomyopathy

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(DCM), the presence of PH is also a predictor of morbidity or mortality.<sup>5</sup> We previously reported that the presence of PH provides valuable prognostic information in ambulatory patients with DCM.<sup>6</sup>

Cardiopulmonary exercise testing (CPX) is an established assessment tool in heart failure (HF) populations.<sup>7</sup> Most often, CPX is used to assess prognosis in HF patients being considered for heart transplantation,<sup>8</sup> and to provide an additional evaluation of disease severity.<sup>7</sup> Given the emerging importance of detecting PH in HF patients and the already established role of CPX in this patient population, examining the ability of this exertional assessment to unmask elevated pulmonary arterial pressure (PAP) is an important research endeavor. CPX has already been proved useful for diagnosing secondary PH in other patients, such as those with hypertrophic cardiomyopathy,<sup>9</sup> or HF.<sup>10,11</sup> However, to our knowledge, there have been no investigations of the impact of CPX variables on PH in DCM. Here, we therefore aimed to evaluate the usefulness of crucial CPX variables for detecting elevated PAP in patients with DCM.

## METHODS

### Study Population

A total of 90 consecutive ambulatory patients with DCM (62 men (69%); mean age  $\pm$  SD, 52  $\pm$  13 years) were enrolled retrospectively in the study at Nagoya University Hospital, Japan. All patients were on optimal pharmacological therapy according to current guidelines for the treatment of HF.<sup>12</sup> Individuals who had suffered an episode of acute HF within the previous month, who had renal dysfunction [estimated glomerular filtration rate (eGFR)  $<30$  mL min<sup>-1</sup> 1.73 m<sup>-2</sup>], or who had received an implanted cardiac resynchronization therapy device or an implantable cardioverter defibrillator before cardiac catheterization were excluded from the study. Echocardiographic findings as a screening tool were left ventricular (LV) dilatation and systolic dysfunction, as defined by depressed LV ejection fraction. DCM was defined by the presence of both an LV ejection fraction of  $<50\%$  (as revealed by contrast left ventriculography) and dilation of the LV cavity in the absence of coronary artery stenosis of  $>50\%$  (as determined by coronary angiography), valvular heart disease, arterial hypertension, and secondary

cardiac muscle disease attributable to any known systemic condition.<sup>13</sup> No patients had histories of acute viral myocarditis or familial DCM, or evidence of immune triggers. The study protocol complied with the Declaration of Helsinki, and written informed consent was obtained from each study patient. The study protocol was approved by the Ethics Review Board of Nagoya University School of Medicine (approval no. 359).

### Study Protocol

Physical examination, laboratory measurements, CPX, and biventricular catheterization were performed within 3 days of study enrollment. All patients were in a stable condition at the time of testing.

### Cardiac Catheterization

All patients initially underwent diagnostic right and left heart catheterization. Patients were in a stable condition at the time of catheterization. For hemodynamic assessment, a 6F Swan-Ganz catheter (Goodman Biosensors, Tokyo, Japan) was inserted by using a jugular approach. Coronary angiography and left ventriculography via the right radial artery were also performed. A 6F fluid-filled pigtail catheter with a high-fidelity micro-manometer (CA-61000-PLB Pressure-tip Catheter; CD Leycom, Zoetermeer, The Netherlands) was positioned in the left ventricle to measure LV pressure. Endomyocardial biopsy was performed in all patients to exclude myocarditis and specific heart muscle disease. Biopsy specimens were obtained from the septal wall of the right ventricle with a 6F biptome.

### Diagnosis of PH

PH was defined hemodynamically as a mean PAP (mPAP) of  $\geq 25$  mmHg at rest, as assessed by right heart catheterization without inhalation of nitric oxide and supplemental oxygen. Mean PAP, mean right atrial pressure, mean pulmonary artery wedge pressure, and the respective oxygen saturations, along with those in the main pulmonary artery, were measured. Cardiac output was assessed by thermodilution and was expressed in liters per minute.

## CPX Procedure

Each patient underwent CPX at a progressively increasing work rate to maximal tolerance on a cycle ergometer. The test protocol was in accordance with the recommendations of the American Thoracic Society and American College of Chest Physicians.<sup>14</sup> The oxygen and carbon dioxide sensors were calibrated before each test by using gases with known oxygen, nitrogen, and carbon dioxide concentrations. The flow sensor was also calibrated before each test by using a 3-L syringe. All patients started at 10 W for a 3-min warm-up, followed by a 10-W/min ramp increment protocol up to the termination criteria. Test termination criteria consisted of patient request, volitional fatigue, ventricular tachycardia,  $\geq 2$  mm horizontal or downsloping ST-segment depression, or a drop in systolic blood pressure (BP) of  $\geq 20$  mmHg during exercise. A qualified exercise physiologist conducted each test, with physician supervision. A 12-lead electrocardiogram was monitored continuously, and BP was measured every minute during exercise and throughout the recovery period. Respiratory gas exchange variables, including  $\text{VO}_2$ ,  $\text{VCO}_2$ , and minute ventilation (VE), were acquired continuously throughout the exercise testing by using an Oxycon Pro ergospirometer (Care Fusion; San Diego, CA, USA); gas-exchange data were obtained breath-by-breath. Peak  $\text{VO}_2$  was expressed as the highest 30-s average value obtained during the last stage of the exercise test, and the peak respiratory exchange ratio was the highest 30-s average value during the last stage of the test. The VE/ $\text{VCO}_2$  slope was determined by using linear regression analysis of the VE and  $\text{VCO}_2$  obtained during exercise.<sup>15</sup> Exercise oscillatory ventilation (EOV) was assessed by using the criteria previously reported by Leite et al.<sup>16</sup> The achieved percentage of predicted peak  $\text{VO}_2$  (%PPeak  $\text{VO}_2$ ) was calculated as [obtained peak  $\text{VO}_2$  / age-, gender-, and weight-adjusted predicted peak  $\text{VO}_2$  in  $\text{mL min}^{-1} \text{kg}^{-1}$ ]  $\times 100$ .<sup>17,18</sup> The ratio of the increase in  $\text{VO}_2$  to the increase in work rate (WR) [ $\Delta\text{O}_2/\Delta\text{WR}$ ] was calculated by least-squares linear regression from the data recorded between 30 s after the start of incremental exercise and 30 s before the end of exercise.

## Statistical Analysis

Data are presented as means  $\pm$  SD. Variables were compared between the DCM with PH and

DCM without PH groups by using Student's *t*-test for unpaired data. The chi-square test was used to assess the significance of differences between dichotomous variables. The impact of mPAP on outcome was analyzed by using the presence or absence of PH as a categorical determinant of adverse events. Other baseline predictors of events were determined by performing univariate Cox proportional hazard regression analysis with age, gender, creatinine, plasma brain natriuretic peptide (BNP), heart rate, cardiac index, systolic BP, LV end-diastolic pressure, pulmonary arterial wedge pressure, pulmonary vascular resistance, peak  $\text{VO}_2$ , and VE/ $\text{VCO}_2$  slope as potential determinants. The hazard ratio and 95% confidence interval were defined. Receiver-operator characteristic (ROC) curve analysis was used to assess the ability of CPX variables to identify subjects with an mPAP  $\geq 25$  mmHg. Binary logistic regression assessed the univariate and multivariate (with  $P < 0.1$ ) ability of CPX variables to identify subjects with mPAP  $\geq 25$  mmHg. All analyses were performed with the SPSS 17.0 software package (SPSS, Chicago, IL, USA). A *P* value of  $< 0.05$  was considered statistically significant.

## RESULTS

### Patient Characteristics

The mean age was 52 years, and 69% of subjects were male. At the time of cardiac catheterization, beta blockers were used by 87% of all patients, angiotensin-converting-enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs) by 86%, diuretics by 69%, and spironolactone by 46%. The mean (25th, 75th percentile) plasma BNP level was 233 (55, 306) pg/mL, and the mean LV ejection fraction was  $30.2 \pm 11.0\%$ .

Clinical characteristics and important hemodynamic parameters of all patients are shown in Table 1. Subjects were allocated to one of two groups on the basis of the absence (DCM without PH group,  $n = 75$ ) or presence (DCM with PH group,  $n = 15$ ) of PH. PH was present in 17% of patients with DCM, and the median (25th, 75th percentile) mPAP for all DCM patients was 17.9 (11.8, 20.0) mmHg. DCM patients with PH were significantly younger than those without PH. Diuretics, beta-blockers, and spironolactone were used significantly more frequently in DCM with PH than in DCM without PH, but there

**Table 1.** Patient Characteristics

	DCM without PH (n = 75)	DCM with PH (n = 15)	P
Age (years)	54 ± 13	45 ± 14	0.038
Male (n, %)	53 (71)	9 (60)	0.459
BMI (kg/m <sup>2</sup> )	23.5 ± 4.2	21.6 ± 4.1	0.133
NYHA	1.57 ± 0.76	2.50 ± 1.23	0.131
Medication			
Diuretics (n, %)	47 (63)	15 (100)	<0.001
ACE-I/ARBs (n, %)	63 (84)	14 (93)	0.753
β-Blockers (n, %)	63 (84)	15 (100)	<0.001
Digitalis (n, %)	9 (12)	9 (17)	0.710
Statins (n, %)	9 (12)	1 (7)	0.669
Amiodarone (n, %)	7 (9)	5 (33)	0.271
Spironolactone (n, %)	29 (39)	12 (80)	0.002
Laboratory			
BNP (pg/mL)	175 (37–274)	550 (178–840)	0.013
eGFR (mL/min/1.73 m <sup>2</sup> )	72 ± 26	74 ± 15	0.707
Hb (mg/dL)	14.0 ± 1.6	14.0 ± 2.3	0.962
T. Chol (mg/dL)	194 ± 34	175 ± 46	0.152
TG (mg/dL)	156 (77–177)	111 (68–152)	0.046
HbA1c (%)	5.74 ± 1.15	5.63 ± 0.80	0.648
Cardiac catheterization			
PAWP (mmHg)	10.0 ± 4.6	25.3 ± 6.9	<0.001
Systolic PAP (mmHg)	24.2 ± 6.8	49.0 ± 15.4	<0.001
Diastolic PAP (mmHg)	9.5 ± 4.0	28.8 ± 10.0	<0.001
Mean PAP (mmHg)	14.4 ± 4.3	35.5 ± 9.6	<0.001
PVR (Wood units)	0.96 ± 0.92	3.25 ± 2.64	0.005
RAP (mmHg)	5.0 ± 3.1	7.7 ± 2.6	0.018
SvO <sub>2</sub> (%)	71.8 ± 5.8	61.8 ± 7.3	0.024
TPG (mmHg)	4.4 ± 4.0	10.3 ± 5.7	0.002
DPG (mmHg)	-0.5 ± -0.6	3.5 ± 3.2	<0.001
Heart rate (bpm)	76.5 ± 13.1	85.0 ± 23.9	0.303
Cardiac output (L/min)	4.73 ± 1.20	3.75 ± 1.46	0.025
Cardiac index (L/min/m <sup>2</sup> )	2.75 ± 0.59	2.27 ± 0.69	0.022
Systolic BP (mmHg)	122 ± 19	104 ± 30	0.051
Diastolic BP (mmHg)	74 ± 12	70 ± 14	0.287
LVEDP (mmHg)	14.4 ± 7.1	25.1 ± 8.8	0.001
LVEDVI (ml/m <sup>2</sup> )	129.5 ± 41.3	183.7 ± 65.4	0.004
LVESVI (ml/m <sup>2</sup> )	90.6 ± 37.8	150.1 ± 59.2	0.004
LVEF (%)	32.0 ± 10.1	22.7 ± 10.4	0.001

Data are presented as mean values ± SD and medians [interquartile range or n (%)].

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; BP = blood pressure; DCM = dilated cardiomyopathy; DPG = diastolic pulmonary vascular gradient; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; LVEDP = LV end-diastolic pressure; LVEDVI = LV end-diastolic volume index; LVESVI = LV end-systolic volume index; LVEF = LV ejection fraction; NYHA = New York Heart Association; PAP = pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SvO<sub>2</sub> = mixed venous oxygen saturation; T. Chol = total cholesterol; TG = triglyceride; TPG = transpulmonary pressure gradient.

were no differences between the 2 groups in the use of ACE-Is or ARBs at the time of cardiac catheterization. Although plasma BNP levels were significantly higher in DCM with PH, eGFR, and serum hemoglobin levels did not differ between the two groups. On cardiac catheterization, the systolic, diastolic, and mean PAP, as well as the pulmonary vascular resistance and right arterial

pressure, were significantly higher in DCM with PH than in DCM without PH, whereas the cardiac index and mixed venous oxygen saturation were significantly lower in the former group. LV end-diastolic pressure, LV end-diastolic volume index, and LV end-systolic volume index were significantly higher, and LV ejection fraction was significantly lower, in DCM with PH.

**Table 2.** Hemodynamic Parameters in Cardiopulmonary Exercise Testing

	DCM without PH (n = 75)	DCM with PH (n = 15)	P
Exercise duration (min)	7.5 ± 2.5	7.1 ± 3.9	0.671
Peak VO <sub>2</sub> (ml/kg/min)	19.2 ± 4.8	11.3 ± 3.6	<0.001
%PPeak VO <sub>2</sub> (%)	72.0 ± 21.8	40.6 ± 12.8	<0.001
VE/VCO <sub>2</sub> slope	29.2 ± 7.4	38.6 ± 9.7	0.002
Peak VO <sub>2</sub> /HR ratio	10.1 ± 4.6	6.9 ± 3.4	0.005
ΔVO <sub>2</sub> /ΔWR	9.7 ± 3.8	5.5 ± 3.1	<0.001
Resting HR (bpm)	85 ± 19	88 ± 17	0.60
Peak HR (bpm)	133 ± 29	117 ± 21	0.019
Resting systolic BP (mmHg)	121 ± 22	111 ± 30	0.212
Peak systolic BP (mmHg)	161 ± 36	131 ± 45	0.026
Resting P <sub>ET</sub> CO <sub>2</sub> (mmHg)	33.3 ± 6.4	30.4 ± 3.7	0.112
EOV	23 (31%)	7 (47%)	0.231
Peak RER	1.09 ± 0.08	1.07 ± 0.11	0.332

BP = blood pressure; HR = heart rate; EOV = exercise oscillatory ventilation; %PPeak VO<sub>2</sub> = achieved percentage of predicted peak VO<sub>2</sub>; P<sub>ET</sub>CO<sub>2</sub> = end-tidal carbon dioxide tension; RER = respiratory exchange ratio; ΔVO<sub>2</sub>/ΔWR = ratio of change in VO<sub>2</sub> to change in work rate.

The CPX variables are shown in Table 2. Although exercise duration did not differ between the two groups, peak VO<sub>2</sub>, %PPeak VO<sub>2</sub>, peak VO<sub>2</sub>/HR ratio, and ΔVO<sub>2</sub>/ΔWR were significantly lower in DCM with PH than in DCM without PH. VE/VCO<sub>2</sub> slope was significantly higher in DCM with PH than in DCM without PH. Although resting HR and resting systolic BP did not differ significantly between the two groups, peak HR and peak systolic BP were significantly lower in DCM with PH than in DCM without PH.

### CPX Variables for Detecting PH

We performed an ROC curve analysis of the ability of peak VO<sub>2</sub>, %PPeak VO<sub>2</sub>, VE/VCO<sub>2</sub> slope, and ΔVO<sub>2</sub>/ΔWR to detect mPAP ≥25 mmHg (Fig. 1). All four diagnostic models were significant for detecting mPAP ≥25 mmHg. A %PPeak VO<sub>2</sub> cutoff value of 52.5% was the best predictor of mPAP ≥25 mmHg in the ROC analysis (area under the curve [AUC: 0.911]; 95% confidence interval [CI]: 0.846 to 0.977, P < 0.001). The sensitivity and specificity of using %PPeakVO<sub>2</sub> to detect PH were 82.8% and 85.7%, respectively. The sensitivity and specificity with a peak VO<sub>2</sub> cutoff value of 13.55 mL kg<sup>-1</sup> min<sup>-1</sup> were 90.6% and 71.4%, respectively (AUC: 0.904; 95% CI: 0.832 to 0.976, P < 0.001). A VE/VCO<sub>2</sub> slope cutoff value of 31.01 had significant diagnostic value (AUC: 0.801; 95% CI: 0.681 to 0.920, P < 0.001), and a ΔVO<sub>2</sub>/ΔWR cutoff value of 7.79 also had significant diagnostic value (AUC:

0.841; 95% CI: 0.714 to 0.968, P < 0.001) for detecting PH.

We used binary logistic regression to assess the independent and combined abilities of CPX variables for detecting PH (Table 3). In the univariate analysis, peak VO<sub>2</sub>, %PPeak VO<sub>2</sub>, peak VO<sub>2</sub>/HR ratio, VE/VCO<sub>2</sub> slope, ΔVO<sub>2</sub>/ΔWR, peak systolic BP, and rest P<sub>ET</sub>CO<sub>2</sub> were significant predictors of PH. In the multivariate analysis, %PPeak VO<sub>2</sub> was the only significant independent predictor of PH (Wald 6.52, odds ratio 0.892, 95% CI 0.818 to 0.974; P = 0.011).

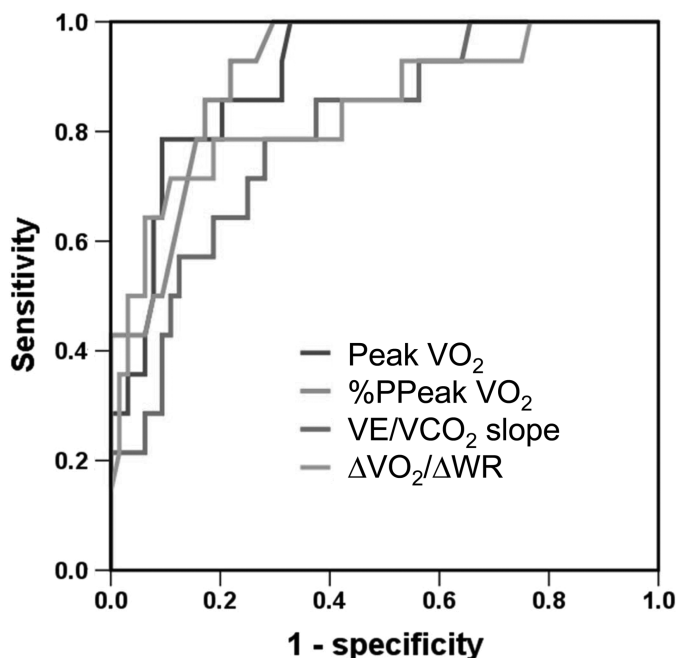
### DISCUSSION

Here, we reported for the first time that reduced %PPeak VO<sub>2</sub> was strongly associated with the presence of PH in patients with DCM. Other CPX variables, including peak VO<sub>2</sub>, VE/VCO<sub>2</sub> slope, and ΔVO<sub>2</sub>/ΔWR, were also useful for detecting the presence of PH. Taken together, these results indicate that CPX variables could be important for diagnosing PH in patients with DCM.

#### Usefulness of Exercise Capacity for Detecting PH in DCM

Four CPX variables, namely peak VO<sub>2</sub>, %PPeak VO<sub>2</sub>, ΔVO<sub>2</sub>/ΔWR, and VE/VCO<sub>2</sub> slope (see Fig. 1), were especially strong predictors of PH. Peak VO<sub>2</sub> and %PPeakVO<sub>2</sub> were superior to the other two as diagnostic markers of increased mPAP. In addition, %PPeak VO<sub>2</sub> was the only significant independent





**Figure 1.** Receiver operating characteristic (ROC) curves showing the ability of cardiopulmonary exercise testing variables to detect pulmonary hypertension (PH). ROC curves of the abilities of peak  $\text{VO}_2$ , %PPeak  $\text{VO}_2$ ,  $\text{VE}/\text{VCO}_2$  slope, and  $\Delta\text{VO}_2/\Delta\text{WR}$  to detect PH (i.e.,  $\text{mPAP} \geq 25$  mmHg). AUC = area under the curve; CI = confidence interval; %PPeak  $\text{VO}_2$  = achieved percentage of predicted peak  $\text{VO}_2$ ; WR = work rate.

**Table 3.** Binary Logistic Analysis for the Detection of Pulmonary Hypertension

Analysis	Univariate				Multivariate			
	Wald	OR	95%CI	P	Wald	OR	95%CI	P
Peak $\text{VO}_2$ (mL/kg/min)	15.1	0.672	0.550–0.821	<0.001				
%PPeak $\text{VO}_2$ (%)	14.0	0.902	0.854–0.952	<0.001	6.52	0.892	0.818–0.974	0.011
Peak $\text{VO}_2/\text{HR}$ ratio	7.13	0.744	0.600–0.924	0.008				
$\text{VE}/\text{VCO}_2$ slope	11.6	1.136	1.056–1.222	0.001				
$\Delta\text{VO}_2/\Delta\text{WR}$	13.9	0.609	0.470–0.790	<0.001				
Peak HR (bpm)	3.81	0.979	0.959–1.000	0.051				
Peak systolic BP (mmHg)	6.62	0.976	0.958–0.994	0.010				
EOV	0.52	1.023	0.726–1.370	0.528				
Rest $\text{P}_{\text{ET}}\text{CO}_2$ (mmHg)	6.99	0.862	0.772–0.962	0.008				
Peak W (watts)	0.47	0.993	0.974–1.013	0.490				

CI = confidence interval; OR = odds ratio. Other abbreviations as in Tables 1 and 2.

predictor of PH by the multivariate logistic analysis (see Table 3).

Peak  $\text{VO}_2$  has traditionally been considered a “gold standard” for selecting candidates for cardiac transplantation.<sup>8</sup> In contrast, %PPeak $\text{VO}_2$  is age-, gender-, and weight-adjusted and is based on directly measured peak  $\text{VO}_2$  during CPX. Furthermore, %PPeak  $\text{VO}_2$  provides important information that can be used for risk stratification of patients with HF.<sup>19</sup> %PPeak  $\text{VO}_2$  and peak

$\text{VO}_2$  had similar abilities to detect PH by ROC analysis, but %PPeak  $\text{VO}_2$  was the only significant independent predictor of PH by the multivariate logistic analysis in our patients.

DCM patients range in age and tend to be younger than other HF patients; this was certainly the case in our DCM patients. The combination of reduced LV ejection fraction and relatively young age at onset suggests that DCM occurrence is at least partly influenced by genetic factors,<sup>20</sup>

although our study did not include genetic profiling to support this hypothesis. These patients are at risk of developing severe, refractory HF. From this perspective, %PPeak  $\text{VO}_2$  might be a more useful predictor of PH than other CPX variables, including peak  $\text{VO}_2$  in DCM because it is adjusted for age.

In patients with HF, the ventilatory parameters in CPX can reflect reactive PH.<sup>11</sup> VE/VCO<sub>2</sub> slope or EOV is important for diagnosing PH in hypertrophic cardiomyopathy,<sup>9</sup> and HF, including with normal ejection fraction,<sup>10</sup> or ischemia.<sup>11</sup> We considered that the main reason for the difference between these studies.<sup>10,11</sup> and our study was different study populations. In addition, the mechanisms behind the occurrence of a steep VE/VCO<sub>2</sub> slope and the presence of EOV are multifactorial. Abnormalities of ventilatory reflex control and pulmonary hemodynamics, as well as the presence of a low cardiac index, during exercise are all possible causes.<sup>16,21,22</sup> In our study, VE/VCO<sub>2</sub> slope (see Fig. 1), but not EOV (AUC: 0.625; 95% CI: 0.427 to 0.823,  $P = 0.211$ ), was a significant parameter for detecting PH in the ROC analysis. Similarly, VE/VCO<sub>2</sub> slope, but not EOV, was a significant predictor of PH in the univariate analysis (see Table 3). EOV was assessed by using the criteria previously reported by Leite et al.<sup>16</sup> Defining EOV can be complex and difficult during exercise; further investigations are needed to determine whether it can be used to detect PH in DCM.

Parameters obtained during submaximal exercise have an advantage over peak  $\text{VO}_2$  in that they can be obtained without maximum effort. In addition, measurement of peak  $\text{VO}_2$  depends on the subject's motivation and is easily influenced by the bias of the investigator.  $\Delta\text{VO}_2/\Delta\text{WR}$  and VE/VCO<sub>2</sub> slope are characterized by the time course of change in respiratory gas variables, reflecting the ability of cardiopulmonary function to adapt to increasing work rate.  $\Delta\text{VO}_2/\Delta\text{WR}$  and VE/VCO<sub>2</sub> slope may therefore, in some regards, be useful in addition to peak  $\text{VO}_2$  for assessing PH.

### Clinical Implications

Exercise tolerance reflects a number of important prognostic factors, including cardiac function, oxygen-carrying capacity, and autonomic nervous system balance.<sup>23-25</sup> CPX is a diagnostic tool used to detect serial changes in exercise capacity. It is of particular benefit for assessing peak  $\text{VO}_2$  and VE/VCO<sub>2</sub> slope in patients with chronic HF, because these parameters function as predictors

of overall mortality or determinants of risk stratification in such individuals.<sup>26-30</sup>

The recognition of PH due to left heart disease has created the need for diagnostic tests to determine when a patient's PAP is elevated. CPX variables have already been evaluated by echocardiography to detect systolic PAP  $\geq 40$  mmHg in an HF population.<sup>10</sup> Determination of systolic PAP echocardiographically by using the sum of the peak RV-RA (right ventricular - right atrial) pressure gradient and the RA pressure has been established as reliable,<sup>31</sup> but additional studies have questioned the accuracy of this relationship, particularly at higher pulmonary artery pressures.<sup>32,33</sup> In patients with very severe tricuspid regurgitation, the Doppler envelope may be truncated because of the early equalization of RV and RA pressures, and using a simplified Bernoulli equation may underestimate the RV-RA gradient.<sup>34</sup>

Here, we examined resting hemodynamic variables, gold standard method, by cardiac catheterization. The use of CPX to diagnose secondary PH has already been demonstrated.<sup>9,35</sup> However, to our knowledge, this is the first study to have investigated the ability of crucial CPX variables to detect elevated PAP.

Currently, there is no specific therapy for PH due to left heart disease. All of our study patients who had DCM with PH used various combinations of diuretics and beta blockers. In addition, 80% of them were using spironolactone at the time of cardiac catheterization; we therefore considered that these patients were optimally medicated. Using CPX to detect PH may lead to early therapeutic interventions for DCM.

### Study Limitations

This was a retrospective study in a single center and with a relatively small sample size. Moreover, hemodynamic diagnosis by challenge tests such as exercise and acute pulmonary vasoreactivity testing was not performed. Finally, the use of single time point measurements did not allow us to assess the time-dependence of PAP in the Cox regression analysis and may have led us to underestimate the prognostic significance of PH.

### CONCLUSIONS

%PPeak  $\text{VO}_2$  was strongly associated with the presence of PH in patients with DCM. Peak  $\text{VO}_2$ ,

VE/VCO<sub>2</sub> slope, and  $\Delta\text{VO}_2/\Delta\text{WR}$  were also useful for detecting the presence of PH. Taken together, these findings indicate that CPX variables could be important for diagnosing PH in patients with DCM.

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## Disclosures

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