

# Cardiopulmonary Exercise Testing Variables Reflect the Degree of Diastolic Dysfunction in Patients With Heart Failure—Normal Ejection Fraction

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- **PURPOSE:** Previous investigations have reported a relationship between variables obtained from echocardiography with tissue Doppler imaging (TDI) and cardiopulmonary exercise testing (CPX) in systolic heart failure (HF) cohorts. The purpose of the present investigation was to perform a comparative analysis between echocardiography with TDI and CPX in patients with HF and normal ejection fraction (NEF).
- **METHODS:** Patients with HF-NEF ( $N = 32$ ) underwent echocardiography with TDI and CPX to determine the following variables: (1) the ratio between mitral early velocity ( $E$ ) and mitral annular velocity ( $E'$ ), (2) ejection fraction, (3) left ventricular (LV) mass, (4) left ventricular end systolic volume, (5) peak oxygen uptake ( $\dot{V}O_2$ ), (6) ventilatory efficiency, (7) the partial pressure of end-tidal carbon dioxide ( $P_{ET}CO_2$ ) at rest and peak exercise, and (8) heart rate recovery at 1 minute ( $HRR_1$ ).
- **RESULTS:** Pearson correlation revealed that  $E/E'$  was significantly correlated with peak oxygen uptake ( $r = -0.55, P = .001$ ), the ventilatory efficiency slope ( $r = 0.60, P < .001$ ), resting  $P_{ET}CO_2$  ( $r = -0.39, P = .03$ ), peak  $P_{ET}CO_2$  ( $r = -0.50, P = .004$ ), and  $HRR_1$  ( $r = -0.63, P < .001$ ). Left ventricular mass and left ventricular end systolic volume were not correlated with any CPX variable. Ejection fraction was correlated with  $HRR_1$  ( $r = -0.55, P = .001$ ). An  $HRR_1$  threshold of less than 16 and/or 16 or more beats per minute (higher value positive) effectively identified subjects with an  $E/E' > 10$  (positive likelihood ratio: 13:2).
- **DISCUSSION:**  $E/E'$  provides an accurate reflection of LV filling pressure and thus, insight into diastolic function. The results of the present investigation indicate CPX provides insight into cardiac dysfunction in patients with HF-NEF and thus, may eventually prove to be a valuable and accepted clinical assessment.

## KEY WORDS

diastolic function  
heart rate recovery  
ventilatory expired gas

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Cardiopulmonary exercise testing (CPX) and echocardiography are cornerstones in the clinical evaluation in patients with systolic heart failure (HF).<sup>1,2</sup> Both assessment techniques provide complementary information, allowing for a more complete assessment of disease severity and functional impairment. However, unlike echocardiography, the clinical value of CPX in

patients with HF and normal ejection fraction (NEF) is not established. While initial evidence indicates that CPX provides prognostic information in patients with NEF,<sup>3</sup> additional diagnostic and prognostic investigations are required to gain clinical acceptance. For example, we are unaware of any previous investigation that has assessed the ability of CPX to reflect the

degree of disease severity in the HF-NEF population (ie, diagnostic potential), an area that has been studied extensively in patients with systolic dysfunction.<sup>4</sup>

Tissue Doppler imaging (TDI) allows for the quantification of additional variables during echocardiography, which appear to provide valuable clinical information, particularly with respect to diastolic function and hence, in the case of HF-NEF, disease severity.<sup>5-7</sup> Of the variables obtained from echocardiography with TDI, the ratio between mitral peak early (*E*) and annular (*E'*) flow velocity, a reflection of left ventricular filling pressure, appears to be particularly valuable. Given the established value of echocardiography with TDI in those with HF-NEF, determination of its relationship to CPX, a well-established clinical assessment technique in its own right, is warranted. Initial research indicates that, in patients with systolic HF, variables obtained from echocardiography with TDI relating to diastolic function are significantly correlated with peak oxygen uptake ( $\dot{V}O_2$ ).<sup>8</sup> While peak  $\dot{V}O_2$  is historically the CPX variable with the greatest degree of clinical recognition, there are a host of other variables demonstrating robust diagnostic and/or prognostic value, including the minute ventilation/carbon dioxide production ( $\dot{V}E/\dot{V}CO_2$ ) slope,<sup>9</sup> the partial pressure of end-tidal carbon dioxide ( $P_{ET}CO_2$ ),<sup>10,11</sup> exercise oscillatory ventilation (EOV),<sup>12</sup> heart rate recovery (HRR),<sup>13</sup> and dyspnea on exertion.<sup>14</sup> These latter variables, individually or as a group, have been scarcely assessed for their diagnostic or prognostic potential in patients with HF-NEF.

The purpose of the present investigation was to examine the ability of CPX to reflect disease severity in patients with HF-NEF, an area that has been thoroughly studied in the systolic HF population. This type of research is needed to determine the value of CPX in HF-NEF, and if results are promising, begin to establish the evidence needed to support utilization in clinical practice. We hypothesize that CPX variables, some of which have been shown to reflect cardiac<sup>4</sup> and pulmonary<sup>15</sup> function in those with systolic HF, will likewise reflect the degree of cardiac dysfunction as assessed by measures obtained from echocardiography with TDI in subjects with HF-NEF.

## METHODS

Thirty-two consecutive subjects with HF-NEF (22 male/10 female, mean age: 62.8 (9.7 years, New York Heart Association class I–III), undergoing evaluation at San Paolo Hospital in Milano, Italy, were enrolled in this study. Sixty-nine percent of subjects had a history of coronary artery disease. All were receiving stable pharmacological management prior to initiation

of the study. Seventy-two percent, 59%, and 38% of the subjects were prescribed an angiotensin-converting enzyme inhibitor,  $\beta$ -blocker, and aldosterone antagonist, respectively. At a maximum, echocardiography with TDI and CPX were performed within 1 week of each other. In 80% of the cohort, both evaluations were performed on the same day. In the minority of cases where assessments were performed on separate days, clinical status and pharmacological regimen remained stable. Inclusion criteria consisted of a left ventricular ejection fraction (LVEF) 50% or more by echocardiography, a previous diagnosis of HF<sup>16</sup> with at least 1 previous hospital admission for acute cardiac decompensation, and the ability to perform maximal exercise testing on an outpatient basis. Informed consent and institutional review board approval was obtained prior to study initiation.

## ECHOCARDIOGRAPHY

Standard M-mode and 2-dimensional echocardiography and Doppler blood flow measurements were performed in agreement with the American Society of Echocardiography guidelines.<sup>17</sup> Septal and posterior left ventricular (LV) wall thickness was obtained from the parasternal long-axis view. Left ventricular end-systolic volumes were obtained from 2-dimensional apical images. Left ventricular end-systolic volume was calculated according to Simpson's method from 2-dimensional apical images. Left ventricular mass was calculated according to the formula proposed by Devereux et al.<sup>18</sup>

### Conventional Doppler and TDI Measurements

Mitral inflow measurements included peak early (*E*) and peak late (*A*) flow velocities and the *E/A* ratio. The TDI of the mitral annulus was obtained from the apical 4-chamber view. A 1.5 sample was placed sequentially at the lateral and septal annular sites. Analysis was performed for the early (*E'*) diastolic peak velocity. The ratio of early transmitral flow velocity to annular mitral velocity of the lateral LV wall (*E/E'*) was taken as an estimate of LV filling pressure.<sup>19</sup>

### Cardiopulmonary Exercise Testing

Each patient performed a supervised progressively increasing (individualized ramp protocol) CPX to maximum tolerance on an electromagnetically braked cycle ergometer. Ventilatory expired gas analysis was obtained using a metabolic cart (Medgraphics CPX-D, Minneapolis, Minnesota). The oxygen and carbon dioxide sensors were calibrated prior to each test using gases with known oxygen, nitrogen, and

carbon dioxide concentrations per manufacturer specifications. The flow sensor was also calibrated before each test using a 3-L syringe. Monitoring consisted of continuous 12-lead electrocardiography, manual blood pressure measurements, and heart rate recordings at every stage via the electrocardiogram. *Peak dyspnea upon exertion* (DOE) was defined as the highest value reported during the last stage of exercise using the 0–10 modified Borg scale, which has been previously validated in patients with asthma.<sup>20</sup>

Test termination criteria consisted of patient request, ventricular tachycardia, 2 mm or more of horizontal or down sloping ST-segment depression, or a drop in systolic blood pressure 20 mm Hg or more during exercise. A qualified exercise physiologist with physician supervision conducted each CPX.  $\dot{V}O_2$  (mL · kg<sup>-1</sup> · min<sup>-1</sup>),  $\dot{V}CO_2$  (L/min),  $\dot{V}E$  (L/min), and  $P_{ET}CO_2$  (mm Hg) were collected continuously at rest and throughout the exercise test. Peak  $\dot{V}O_2$  was expressed as the highest 30-second average value obtained during the last stage of the exercise test. Peak respiratory exchange ratio was the highest 30-second averaged value during the last stage of the test. Ten-second averaged  $\dot{V}E$  and  $\dot{V}CO_2$  data, from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp, Bellevue, Washington) to calculate the  $\dot{V}E/\dot{V}CO_2$  slope via least squares linear regression ( $y = mx + b$ ,  $m =$  slope). This calculation method for the  $\dot{V}E/\dot{V}CO_2$  slope has been shown to produce clinically optimal information compared with derivations excluding data past the respiratory compensation point.<sup>4</sup> Resting  $P_{ET}CO_2$  was the 2-minute averaged value in the seated position prior to exercise, while the peak value was expressed as the highest 30-second average value obtained during the last stage of the exercise test. *Exercise oscillatory ventilation* was defined as an oscillatory pattern at rest which persisted for 60% or more of the exercise test at an amplitude 15% or more of the average resting value.<sup>12,21,22</sup> *Heart rate recovery* was defined as the difference between the values obtained at peak exercise and at 1-minute recovery during active cool-down ( $HRR_1$ ).

### Statistical Analysis

Continuous variables are reported as mean ± standard deviation. Pearson product-moment correlation was used to assess the relationships between echocardiography with TDI and continuous CPX variables. The Spearman  $\rho$  assessed the relationship between echocardiography with TDI and peak DOE. Unpaired *t* testing was used to compare differences in echocardiography with TDI variables according to the presence or absence of EOV. Receiver operating characteristic (ROC) curves, a statistical technique used to

determine variable ability (in this case CPX) to discriminate between normal and abnormal “gold-standard” characteristics, were constructed for CPX variables to determine their ability to distinguish between an  $E/E' \leq$  or  $>10$ , which has been found to accurately distinguish between normal and elevated pulmonary capillary wedge pressure.<sup>23,24</sup> Area under the ROC curve (range, 0–1.0) indicates the discriminatory value of a predictor variable with a value of 1.0 equating to 100% accuracy in sensitivity (ie, subjects with an  $E/E' >10$ ) and specificity (ie, subjects with an  $E/E' \leq 10$ ). Contingency tables were used to determine the positive likelihood ratio for an  $E/E' >10$  based upon ROC curve-established CPX thresholds. Statistical differences with a *P* less than .05 were considered significant.

## RESULTS

Echocardiography with TDI and CPX characteristics for the overall group are listed in Table 1. Mean LVEF was within the normal range, and the mean  $E/E'$  ratio was less than 10 consistent with normal left ventricular filling pressure.<sup>19</sup> A mean peak respiratory exchange ratio more than 1.0 indicates good subject effort during CPX. Mean peak  $\dot{V}O_2$  and  $P_{ET}CO_2$  were

**Table 1 • ECHOCARDIOGRAPHY WITH TDI AND CPX CHARACTERISTICS**

Echocardiography with TDI	
LVEF, %	55.4 ± 4.4
LVESV, mL	95.2 ± 34.5
LV mass, g	217.8 ± 24.8
<i>E</i> , cm/s	68.3 ± 16.0
<i>E'</i> , cm/s	8.7 ± 3.1
<i>A</i> , cm/s	51.4 ± 9.1
<i>E/A</i> ratio	1.4 ± 0.30
<i>E/E'</i> ratio	8.8 ± 3.4
Echocardiography with CPX	
Peak $\dot{V}O_2$ , mL · kg <sup>-1</sup> · min <sup>-1</sup>	14.5 ± 5.6
Peak RER	1.07 ± 0.11
$\dot{V}E/\dot{V}CO_2$ slope	34.0 ± 9.0
$P_{ET}CO_2$ at rest, mm Hg	34.3 ± 3.8
$P_{ET}CO_2$ at peak exercise, mm Hg	33.5 ± 5.1
EOV (% of subjects)	41
$HRR_1$ , beats per min	18 ± 3

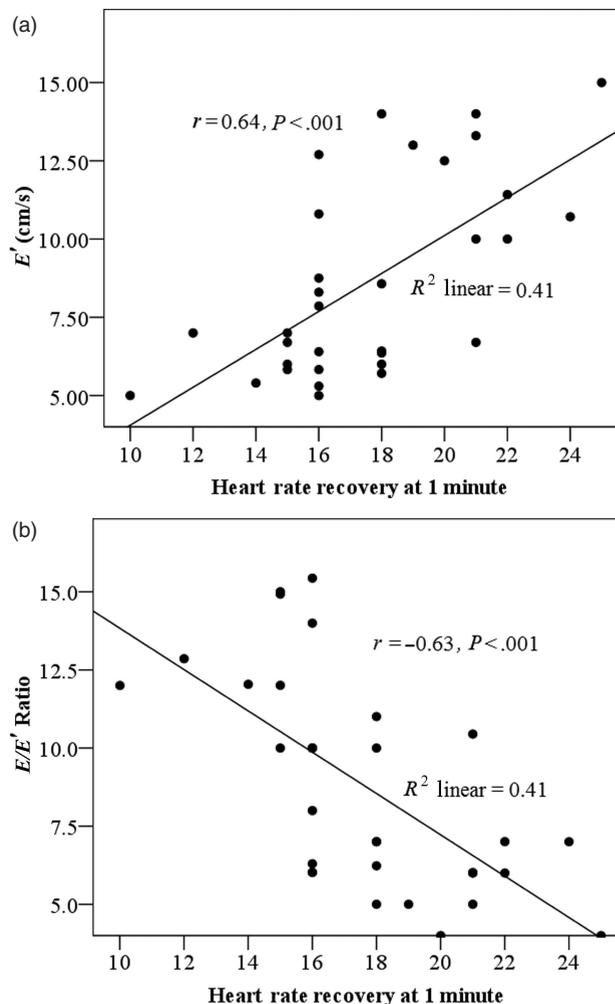
Abbreviations: TDI, tissue Doppler imaging; CPX, cardiopulmonary exercise testing; LVEF, left ventricular ejection fraction; CPX, cardiopulmonary exercise testing; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LV, left ventricular; *E*, mitral peak velocity of early filling; *E'*, early diastolic mitral annular velocity; *A*, mitral peak velocity of late filling;  $\dot{V}O_2$ , oxygen uptake; RER, respiratory exchange ratio;  $\dot{V}E/\dot{V}CO_2$ , minute ventilation/carbon dioxide production;  $P_{ET}CO_2$ , partial pressure of end-tidal carbon dioxide; EOV, exercise oscillatory ventilation;  $HRR_1$ , heart rate recovery at 1 minute.

below normally expected values, while the mean  $\dot{V}_E/\dot{V}_{CO_2}$  slope was above the normal threshold of 30.<sup>4</sup> Moreover, a large percentage of subjects presented with EOv during exercise. Collectively, these CPX characteristics possess similarities to what has been found in cohorts with systolic HF.

Results from the correlation analysis between echocardiography with TDI and CPX variables are presented in Table 2. All CPX variables were correlated with  $E'$  and the  $E/E'$  ratio. The relationship between  $E'$  and both  $HRR_1$  and peak DOE was the strongest compared with all other CPX variables. The most robust linear correlation with the  $E/E'$  ratio was again  $HRR_1$ . The correlation between  $HRR_1$  and both  $E'$  and the  $E/E'$  ratio are illustrated in Figures 1a and 1b, respectively. Both peak  $\dot{V}O_2$  and the  $\dot{V}_E/\dot{V}_{CO_2}$  slope were significantly correlated with the  $A$  flow velocity, while the relationship between LVEF and both  $HRR_1$  and peak DOE reached statistical significance. All other correlations between echocardiography with TDI and CPX did not reach statistical significance.

Unpaired  $t$  testing results for echocardiography with TDI variables according to the absence or presence of EOv are listed in Table 3. The  $E/E'$  ratio and LVEF were significantly higher, while  $E'$  was significantly lower in subjects who demonstrated EOv during CPX.

Receiver operating characteristic curve analysis examining the ability of CPX variables to identify subjects with an  $E/E'$  ratio of more than 10 is listed in Table 4. With the exception of EOv, the area under the ROC curve was significant for all other variables. The positive likelihood ratio for an  $E/E'$  ratio of more than 10 was highest in subjects with an  $HRR_1$  of less than 16 beats per minute, followed by a  $\dot{V}_E/\dot{V}_{CO_2}$  slope



**Figure 1.** Scatter plot for  $HRR_1$  and both  $E'$  and the  $E/E'$  ratio. (a)  $HRR_1$  and  $E'$ . (b)  $HRR_1$  and  $E/E'$ .  $HRR_1$  indicates heart rate recovery at 1 minute;  $E$ , mitral peak velocity of early filling;  $E'$ , early diastolic mitral annular velocity.

**Table 2 • PEARSON PRODUCT-MOMENT AND SPEARMAN CORRELATION RESULTS BETWEEN ECHOCARDIOGRAPH WITH TDI AND CPX VARIABLES**

	LVEF (%)	LV mass, g	LVESV, mL	$E$ , cm/s	$A$ , cm/s	$E'$ , cm/s	$E/A$	$E/E'$
Peak $\dot{V}O_2$ , $mL \cdot kg^{-1} \cdot min^{-1}$	-0.35 $P = .05$	-0.18 $P = .32$	0.12 $P = 0.50$	-0.93 $P = .61$	-0.55 <sup>a</sup> $P = .001$	0.58 <sup>a</sup> $P = .001$	0.32 $P = .07$	-0.55 <sup>a</sup> $P = .001$
$\dot{V}_E/\dot{V}_{CO_2}$ slope	0.14 $P = .451$	0.18 $P = .33$	-0.07 $P = 0.69$	0.27 $P = .13$	0.37 <sup>a</sup> $P = .04$	-0.43 <sup>a</sup> $P = .01$	0.02 $P = .90$	0.60 <sup>a</sup> $P = .00$
$P_{Et}CO_2$ at rest, mm Hg	-0.23 $P = .21$	-0.25 $P = .17$	-0.11 $P = 0.54$	-0.23 $P = .21$	-0.19 $P = .30$	0.25 <sup>a</sup> $P = .17$	-0.12 $P = .52$	-0.39 <sup>a</sup> $P = .03$
$P_{Et}CO_2$ at peak exercise, mm Hg	-0.26 $P = .15$	-0.23 $P = .21$	-0.19 $P = 0.52$	-0.22 $P = .22$	-0.19 $P = .30$	0.39 <sup>a</sup> $P = .03$	-0.09 $P = .62$	-0.50 <sup>a</sup> $P = .004$
$HRR_1$ , beats per min	-0.55 <sup>a</sup> $P = .001$	-0.05 $P = .79$	0.14 $P = 0.45$	-0.17 $P = .35$	-0.29 $P = .11$	0.64 <sup>a</sup> $P = .001$	0.08 $P = .68$	-0.63 <sup>a</sup> $P = .001$
Peak DOE (0-10)	0.42 <sup>a</sup> $P = .02$	-0.08 $P = .68$	-0.18 $P = .32$	0.01 $P = .94$	0.13 $P = .50$	-0.64 <sup>a</sup> $P = .001$	-0.15 $P = .41$	0.60 <sup>a</sup> $P = .001$

Abbreviations: TDI, tissue Doppler imaging; CPX, cardiopulmonary exercise testing; LVEF, left ventricular ejection fraction; LV, left ventricular; LVESV, left ventricular end systolic volume;  $E$ , mitral peak velocity of early filling;  $E'$ , early diastolic mitral annular velocity;  $A$ , mitral peak velocity of late filling;  $\dot{V}O_2$ , oxygen uptake;  $\dot{V}_E/\dot{V}_{CO_2}$ , minute ventilation/carbon dioxide production;  $P_{Et}CO_2$ , partial pressure of end-tidal carbon dioxide;  $HRR_1$ , heart rate recovery at 1 minute; DOE, dyspnea upon exertion.

<sup>a</sup> Statistically significant.

**Table 3 • COMPARISON OF ECHOCARDIOGRAPHY WITH TDI VARIABLES ACCORDING TO THE PRESENCE OR ABSENCE OF EOVS**

	No EOVS ( <i>n</i> = 19)	EOVS ( <i>n</i> = 13)
LVEF, %	53.9 ± 4.0	57.8 ± 4.2 <sup>a</sup>
LVESV, mL	103.6 ± 17.4	82.9 ± 48.5
LV mass, g	218.6 ± 21.0	216.5 ± 30.5
<i>E</i> , cm/s	64.7 ± 10.7	73.6 ± 20.9
<i>E'</i> , cm/s	10.3 ± 3.1	6.4 ± 1.1 <sup>b</sup>
<i>A</i> , cm/s	48.9 ± 6.5	55.0 ± 11.3
<i>E/A</i> ratio	1.4 ± 0.23	1.4 ± 0.39
<i>E/E'</i> ratio	6.9 ± 2.3	11.6 ± 2.8 <sup>b</sup>

Abbreviations: TDI, tissue Doppler imaging; EOVS, exercise oscillatory ventilation; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LV, left ventricular; *E*, mitral peak velocity of early filling; *E'*, early diastolic mitral annular velocity; *A*, mitral peak velocity of late filling.

<sup>a</sup>*P* < .05.

<sup>b</sup>*P* < .001.

of 36 or more. The positive likelihood ratios for all other CPX variables were substantially lower and similar. For the 3 subjects presenting with an *E/E'* ratio at or above 15, all presented with EOVS and a  $\dot{V}_E/\dot{V}_{CO_2}$  slope of more than 36. Two of the 3 subjects presented with an HRR<sub>1</sub> less than 16 beats per minute, a peak  $\dot{V}O_2$  (12 mL · kg<sup>-1</sup> · min<sup>-1</sup>, a resting P<sub>ET</sub>CO<sub>2</sub> < 33 mm Hg, and a peak DOE ≥ 7. Only 1 of the 3 subjects presented with a peak P<sub>ET</sub>CO<sub>2</sub> < 33 mm Hg.

## DISCUSSION

To our knowledge, this is the first investigation to examine the relationship between cardiac function, assessed by echocardiography with TDI and CPX in an HF-NEF cohort. The results presented here allow us to

confirm our alternate hypothesis that key CPX variables reflect the degree of cardiac dysfunction assessed by measures obtained from echocardiography with TDI in HF-NEF. Our results are consistent in several respects with previous investigations examining the relationship between echocardiography with TDI and CPX in patients with systolic HF. Terzi et al<sup>8</sup> reported a significant correlation (*P* < .05) between both *E'* and the *E/E'* ratio and peak  $\dot{V}O_2$  in 59 subjects with systolic HF. In a separate systolic HF cohort (*n* = 53), Hadano et al<sup>25</sup> likewise found a significant correlation (all *P* < .01) between peak  $\dot{V}O_2$  and both *E'* and *E/E'*, again in agreement with the present investigation.

While peak  $\dot{V}O_2$  has retained the highest level of clinical recognition, a host of other CPX variables have demonstrated significant diagnostic and prognostic values, including the  $\dot{V}_E/\dot{V}_{CO_2}$  slope,<sup>9,26</sup> HRR,<sup>27</sup> EOVS,<sup>21,28</sup> P<sub>ET</sub>CO<sub>2</sub>,<sup>11,29</sup> and peak DOE.<sup>14</sup> Moreover, it appears a number of the aforementioned CPX variables prognostically and diagnostically outperform peak  $\dot{V}O_2$  in patients with HF.<sup>4,27,30,31</sup> It appears that the present investigation is the first to examine the relationship between echocardiography with TDI and CPX variables in any HF cohort. In addition to peak  $\dot{V}O_2$ , all CPX variables assessed were significantly correlated with *E'* and the *E/E'* ratio, indicating that a poorer CPX response is reflective of worsening LV diastolic function in patients with HF-NEF. It does appear that HRR<sub>1</sub> demonstrated the strongest relationship with both *E'* and the *E/E'* ratio. In addition, while all but 1 CPX variable demonstrated significant diagnostic classification schemes, an HRR<sub>1</sub> threshold of less than 16 beats per minute most effectively identified subjects with an *E/E'* ratio of more than 10. Interestingly, this same HRR<sub>1</sub> threshold may be prognostically optimal in patients with systolic HF.<sup>27</sup> The same threshold trends for the  $\dot{V}_E/\dot{V}_{CO_2}$  slope and resting P<sub>ET</sub>CO<sub>2</sub> were also found in the present investigation

**Table 4 RECEIVER OPERATING CHARACTERISTIC CURVE ANALYSIS USING CPX VARIABLES TO IDENTIFY SUBJECTS WITH AN *E/E'* > 10**

	Area under ROC curve	95% CI	Optimal diagnostic threshold <sup>a</sup>	<i>P</i> for area under ROC curve	Positive likelihood ratio	95% CI
Peak $\dot{V}O_2$ , mL · kg <sup>-1</sup> · min <sup>-1</sup>	0.73	0.52–0.93	<12	.04	2.6	1.1–6.6
$\dot{V}_E/\dot{V}_{CO_2}$ slope	0.83	0.65–1.0	≥36	.003	5.0	2.0–12.3
P <sub>ET</sub> CO <sub>2</sub> at rest, mm Hg	0.73	0.51–0.94	<33	.04	2.6	1.2–5.7
P <sub>ET</sub> CO <sub>2</sub> at peak exercise, mm Hg	0.82	0.64–0.99	<33	.005	2.2	1.1–4.6
EOVS	0.71	0.51–0.91	Present	.06	2.6	1.2–5.7
HRR <sub>1</sub> , beats per min	0.83	0.66–1.0	<16	.003	13.2	1.9–95.7
Peak DOE (0–10)	0.73	0.55–0.91	≥7	.04	2.2	1.1–4.6

Abbreviations: CPX, cardiopulmonary exercise testing; *E*, mitral peak velocity of early filling; *E'*, early diastolic mitral annular velocity;  $\dot{V}O_2$ , oxygen uptake;  $\dot{V}_E/\dot{V}_{CO_2}$ , minute ventilation/carbon dioxide production; P<sub>ET</sub>CO<sub>2</sub>, partial pressure of end-tidal carbon dioxide, EOVS, exercise oscillatory ventilation; HRR<sub>1</sub>, heart rate recovery at 1 min; DOE, dyspnea upon exertion.

<sup>a</sup>Defined variable unit threshold values represent abnormal response.

where values  $\geq 36$ <sup>32</sup> or less and less than  $33$ <sup>11</sup> have been shown to indicate greater risk for adverse events in patients with systolic HF. Previous research has found that a multivariate approach to CPX variables, combining peak  $\dot{V}O_2$ , the  $\dot{V}_E/\dot{V}_{CO_2}$  slope, resting  $P_{ET,CO_2}$ , and  $HRR_1$ , provides optimal prognostic resolution in patients with systolic HF.<sup>33</sup> This finding is attributed to the fact that different CPX variables are, to a degree, reflective of unique pathophysiological mechanisms. Thus, while  $HRR_1$  demonstrated the strongest correlation with  $E/E'$  in the present investigation, a multivariate CPX approach may ultimately prove to be clinically optimal.

These findings collectively indicate that threshold values used to define an abnormal CPX response for diagnostic and/or prognostic purposes in the systolic HF population may likewise be clinically applicable in patients with HF-NEF, providing insight into the degree of disease severity. As stated at the onset, the use of CPX in the clinical assessment of patients with HF-NEF is scarce, which is in large part attributed to the lack of scientific evidence supporting its use. The present investigation begins to lay the foundation supporting CPX in this HF group by demonstrating that this exercise assessment provides insight into the degree of diastolic dysfunction found in these patients.

The significant correlation between both peak DOE and  $HRR_1$  and LVEF indicates that higher values for this echocardiography variable were reflected by poorer exercise performance, which was not necessarily an expected finding. While not reaching statistical significance, this appeared to be the trend between other CPX variables and LVEF. These findings may indicate a higher LVEF in subjects with confirmed HF secondary to diastolic dysfunction and reflects a higher level of disease severity; that is, subjects with a higher LVEF may present with a less compliant LV and therefore a lower-end diastolic volume and cardiac output. As a *post hoc* analysis to support this hypothesis, we examined the correlation between  $E'$ , an indicator of LV compliance, and LVEF finding a significant relationship ( $r = -0.38$ ,  $P = .03$ ). The correlation between  $A$  flow velocity and both peak  $\dot{V}O_2$  and the  $\dot{V}_E/\dot{V}_{CO_2}$  slope was also not expected. This relationship may also be an indication of worsening LV compliance, reflected by a higher late  $A$  flow velocity and hence deteriorating exercise performance.

Cardiopulmonary exercise testing variables clearly demonstrated the strongest relationship with  $E'$  and the  $E/E'$  ratio in the present investigation. Both of the aforementioned echocardiography with TDI variables provide insight into diastolic function through their reflection of LV relaxation and filling

pressure, respectively. The pathophysiological link explaining the link between CPX variables and both  $E'$  and the  $E/E'$  ratio is likely multifactorial. Stein et al<sup>34</sup> recently demonstrated a relationship between diastolic dysfunction and heightened sympathetic tone in patients with HF. Given the relationship between  $HRR$  and autonomic tone,<sup>35</sup> the correlation of this exercise variable to both  $E'$  and the  $E/E'$  ratio, markers of diastolic dysfunction, is not surprising. Ventilatory dysfunction during exercise in HF, central to the frequently observed elevation in the  $\dot{V}_E/\dot{V}_{CO_2}$  slope as well as  $EOV$ , has likewise been linked to autonomic abnormalities favoring increased sympathetic tone.<sup>36</sup> In addition, abnormal elevations in the  $\dot{V}_E/\dot{V}_{CO_2}$  slope and peak DOE as well as diminished  $P_{ET,CO_2}$  and peak  $\dot{V}O_2$  values have all been previously linked to increasing pressure in the pulmonary vasculature,<sup>26,37,38</sup> a condition that can be precipitated by LV diastolic dysfunction.<sup>39</sup> Such an elevation in pulmonary pressure (1) leads to ventilation-perfusion abnormalities, thereby negatively impacting the gas-exchange response during exercise, and (2) accentuates the sensation of dyspnea. Therefore, although it is not possible to assign percentage contributions to each unique pathophysiological process, both autonomic dysfunction and elevated pulmonary pressure serve as plausible factors accounting for the link between diastolic dysfunction and an abnormal CPX response in patients with HF-NEF.

The small sample size of the present investigation is an apparent limitation. However, the fact that this study appears to be the first to analyze the relationship between echocardiography with TDI and CPX in patients with HF-NEF does add to its novelty, thus providing an important contribution to the literature. However, this type of analysis must be repeated in separate HF-NEF cohorts before more definitive conclusions regarding the ability of CPX to reflect disease severity are drawn.

In conclusion, the present investigation appears to be the first to assess a comprehensive list of variables obtained from echocardiography with TDI and CPX in patients with HF-NEF. Similar to previous investigations in patients with systolic HF,<sup>4</sup> it appears that the CPX response likewise provides a reflection of cardiac, specifically diastolic, dysfunction in a cohort with HF-NEF. Future investigations are needed to more clearly define the clinical role of CPX in this important HF subgroup.

## References

1. Hunt SA, Abraham WT, Chin MH, et al. ACC(AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of

- Cardiology/American Heart Association Task Force on practice guidelines (writing committee to update the 2001 guidelines for the evaluation and management of heart failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*. 2005;112:e154–e235.
2. Gibbons RJ, Balady GJ, Timothy BJ, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to update the 1997 exercise testing guidelines). *J Am Coll Cardiol*. 2002;40:1531–1540.
  3. Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol*. 2005;46:1883–1890.
  4. Arena R, Myers J, Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart Fail Rev*. 2008;13:245–269.
  5. Hamdan A, Shapira Y, Bengal T, et al. Tissue Doppler imaging in patients with advanced heart failure: relation to functional class and prognosis. *J Heart Lung Transplant*. 2006;25:214–218.
  6. Bruch C, Rothenburger M, Gotzmann M, et al. Chronic kidney disease in patients with chronic heart failure—impact on intracardiac conduction, diastolic function and prognosis. *Int J Cardiol*. 2007;118:375–380.
  7. Gradaus R, Stuckenberg V, Loher A, et al. Diastolic filling pattern and left ventricular diameter predict response and prognosis after cardiac resynchronization therapy. *Heart*. 2008;94:1026–1031.
  8. Terzi S, Sayar N, Bilsel T, et al. Tissue Doppler imaging adds incremental value in predicting exercise capacity in patients with congestive heart failure. *Heart Vessels*. 2007;22:237–244.
  9. Francis DP, Shamim W, Davies LC, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2)slope and peak VO(2). *Eur Heart J*. 2000;21:154–161.
  10. Matsumoto A, Itoh H, Eto Y, et al. End-tidal CO<sub>2</sub> pressure decreases during exercise in cardiac patients: association with severity of heart failure and cardiac output reserve. *J Am Coll Cardiol*. 2000;36:242–249.
  11. Arena R, Myers J, Abella J, et al. The partial pressure of resting end-tidal carbon dioxide predicts major cardiac events in patients with systolic heart failure. *Am Heart J*. 2008;156:982–988.
  12. Guazzi M, Arena R, Ascione A, Piepoli M, Guazzi MD. Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value. *Am Heart J*. 2007;153:859–867.
  13. Arena R, Guazzi M, Myers J, Peberdy MA. Prognostic value of heart rate recovery in patients with heart failure. *Am Heart J*. 2006;151:851.e7–e13.
  14. Chase P, Arena R, Myers J, et al. Prognostic usefulness of dyspnea versus fatigue as reason for exercise test termination in patients with heart failure. *Am J Cardiol*. 2008;102:879–882.
  15. Reindl I, Kleber FX. Exertional hyperpnea in patients with chronic heart failure is a reversible cause of exercise intolerance. *Basic Res Cardiol*. 1996;91(suppl 1):37–43.
  16. Radford MJ, Arnold JM, Bennett SJ, et al. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with chronic heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (writing committee to develop heart failure clinical data standards): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Failure Society of America. *Circulation*. 2005;112:1888–1916.
  17. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC(AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE committee to update the 1997 Guidelines for the Clinical Application of Echocardiography). *Circulation*. 2003;108:1146–1162.
  18. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57:450–458.
  19. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. *Circulation*. 2000;102:1788–1794.
  20. Burdon JG, Juniper EF, Killian KJ, Hargreave FE, Campbell EJ. The perception of breathlessness in asthma. *Am Rev Respir Dis*. 1982;126:825–828.
  21. Corra U, Giordano A, Bosimini E, et al. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. *Chest*. 2002;121:1572–1580.
  22. Corra U, Pistono M, Mezzani A, et al. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. *Circulation*. 2006;113:44–50.
  23. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol*. 1997;30:1527–1533.
  24. Nagueh SF, Mikati I, Kopelen HA, Middleton KJ, Quinones MA, Zoghbi WA. Doppler estimation of left ventricular filling pressure in sinus tachycardia: a new application of tissue Doppler imaging. *Circulation*. 1998;98:1644–1650.
  25. Hadano Y, Murata K, Yamamoto T, et al. Usefulness of mitral annular velocity in predicting exercise tolerance in patients with impaired left ventricular systolic function. *Am J Cardiol*. 2006;9:1025–1028.
  26. Reindl I, Wernecke KD, Opitz C, et al. Impaired ventilatory efficiency in chronic heart failure: possible role of pulmonary vasoconstriction. *Am Heart J*. 1998;136:778–785.
  27. Arena R, Myers J, Abella J, et al. The prognostic value of the heart rate response during exercise and recovery in patients with heart failure: influence of  $\beta$ -blockade. *Int J Cardiol*. 2010;138:166–173.
  28. Guazzi M, Arena R, Ascione A, Piepoli M, Guazzi MD. Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value. *Am Heart J*. 2007;153:859–867.
  29. Arena R, Peberdy MA, Myers J, Guazzi M, Tevald M. Prognostic value of resting end-tidal carbon dioxide in patients with heart failure. *Int J Cardiol*. 2006;109:351–358.
  30. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. *Eur Heart J*. 2008;29:2751–2759.
  31. Myers J, Arena R, Dewey F, et al. A cardiopulmonary exercise testing score for predicting outcomes in patients with heart failure. *Am Heart J*. 2008;156:1177–1183.
  32. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. *Circulation*. 2007;115:2410–2417.
  33. Myers J, Arena R, Dewey F, et al. A cardiopulmonary exercise testing score for predicting outcomes in patients with heart failure. *Am Heart J*. 2008;156:1177–1183.
  34. Stein PK, Tereshchenko L, Domitrovich PP, Kleiger RE, Perez A, Deedwania P. Diastolic dysfunction and autonomic

- abnormalities in patients with systolic heart failure. *Eur J Heart Fail.* 2007;9:364–369.
35. Pierpont GL, Voth EJ. Assessing autonomic function by analysis of heart rate recovery from exercise in healthy subjects. *Am J Cardiol.* 2004;94:64–68.
  36. Narkiewicz K, Pesek CA, van de Borne PJH, Kato M, Somers VK. Enhanced sympathetic and ventilatory responses to central chemoreflex activation in heart failure. *Circulation.* 1999;100:262–267.
  37. Yasunobu Y, Oudiz RJ, Sun XG, Hansen JE, Wasserman K. End-tidal PCO<sub>2</sub> abnormality and exercise limitation in patients with primary pulmonary hypertension. *Chest.* 2005;127:1637–1646.
  38. Arques S, Roux E, Luccioni R. Current clinical applications of spectral tissue Doppler echocardiography ( $E/E'$  ratio) as a noninvasive surrogate for left ventricular diastolic pressures in the diagnosis of heart failure with preserved left ventricular systolic function. *Cardiovasc Ultrasound.* 2007;5:16.
  39. Straburzynska-Migaj E, Szyszka A, Trojnarska O, Cieslinski A. Restrictive filling pattern predicts pulmonary hypertension and is associated with increased BNP levels and impaired exercise capacity in patients with heart failure. *Kardiol Pol.* 2007;65:1049–1055.