A novel cardiopulmonary exercise test protocol and criterion to determine maximal oxygen uptake in chronic heart failure

T. Scott Bowen,1 Daniel T. Cannon,1 Gordon Begg,2 Vivek Baliga,2 Klaus K. Witte,2 and Harry B. Rossiter1,3

1Institute of Membrane and Systems Biology, 2Division of Cardiovascular and Diabetes Research, University of Leeds, Leeds, United Kingdom; and 3Division of Respiratory and Critical Care Physiology and Medicine, Los Angeles Biomedical Research Institute at Harbor-University of California Los Angeles Medical Center, Torrance, California

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Bowen TS, Cannon DT, Begg G, Baliga V, Witte KK, Rossiter HB. A novel cardiopulmonary exercise test protocol and criterion to determine maximal oxygen uptake in chronic heart failure. J Appl Physiol 113: 451–458, 2012. First published May 31, 2012; doi:10.1152/japplphysiol.01416.2011.—Cardiopulmonary exercise testing for peak oxygen uptake (V˙O2peak) can evaluate prognosis in chronic heart failure (CHF) patients, with the peak respiratory exchange ratio (RERpeak) commonly used to confirm maximal effort and maximal oxygen uptake (V˙O2max). We determined the precision of RERpeak in confirming V˙O2max, and whether a novel ramp-incremental (RI) step-exercise (SE) (RISE) test could better determine V˙O2max in CHF. Male CHF patients (n = 24; NYHA class I–III) performed a symptom-limited RISE-95 cycle ergometer test in the format: RI (4–18 W/min; ~10 min); 5 min recovery (10 W); SE (95% peak RI work rate). Patients (n = 18) then performed RISE-95 tests using slow (3–8 W/min; ~15 min) and fast (10–30 W/min; ~6 min) ramp rates. Pulmonary gas exchange was measured breath-by-breath. V˙O2peak was compared within patients by unpaired t-test of the highest 12 breaths during RI and SE phases to confirm V˙O2max and its 95% confidence limits (Cl95). RERpeak was significantly influenced by ramp rate (fast, medium, slow: 1.21 ± 0.1 vs. 1.15 ± 0.1 vs. 1.09 ± 0.1; P = 0.001), unlike V˙O2peak (mean n = 18; 14.4 ± 2.6 ml·kg−1·min−1; P = 0.476). Group V˙O2peak was similar between RI and SE (n = 24; 14.5 ± 3.0 vs. 14.7 ± 3.1 ml·kg−1·min−1; P = 0.407); however, within-subject comparisons confirmed V˙O2max and its 95% confidence limits (Cl95) for V˙O2max estimation averaged 1.4 ± 0.8 ml·kg−1·min−1. The RERpeak in CHF was significantly influenced by ramp rate, suggesting its use to determine maximal effort and V˙O2max be abandoned. In contrast, the RISE-95 test had high precision for V˙O2max confirmation with patient-specific Cl95 (without secondary criteria), and showed V˙O2max was commonly underestimated in CHF. The RISE-95 test was well tolerated by CHF patients, supporting its use for V˙O2max confirmation.

EXERCISE INTOLERANCE and cardiac dysfunction characterize the syndrome of chronic heart failure (CHF). A treadmill or cycle ergometer-based peak exercise test, with noninvasive cardiopulmonary measurements for the determination of peak oxygen uptake (V˙O2peak), is the most widely used measure of physiological limitation in CHF, providing information on the degree of physiological dysfunction, symptoms, and prognosis (20). A V˙O2peak ≤ 14 ml·kg−1·min−1 is associated with increased mortality in CHF (20) and is a key criterion in the algorithm for cardiac transplant listing (21). Hence, accurate and reliable determination of the physiological limit of O2 transport and utilization is crucial to guide treatment in CHF patients.

Peak exercise testing, however, is commonly symptom-limited in CHF patients due to breathlessness and fatigue. Thus many patients voluntarily terminate exercise at a V˙O2peak before reaching the maximum physiological limit of O2 delivery and utilization [V˙O2max (37)], such that the best index of aerobic capacity and integrated neuromuscular-cardiopulmonary function (29) remains underestimated. Additionally, distinguishing between the cardiopulmonary dynamics of maximal or submaximal exercise tests is extremely complex [i.e., the incidence of a plateau, or not, in the V˙O2-to-work rate relationship (9, 14)], such that the objective data collected often do not allow a submaximal V˙O2peak to be discriminated from a V˙O2max. Therefore, corroborating criteria (15) from the responses of blood lactate (values > 8 mM), heart rate (to within 10% of age-predicted maximum), ratings of perceived exertion (Borg scale RPE values > 18) or the end-exercise peak respiratory exchange ratio (RERpeak > 1.00–1.15) have each been used to confirm whether J patients have provided a maximum effort; and 2) the measured V˙O2peak is representative of V˙O2max.

The utility of these secondary measures has been shown to be limited at best (15) and may even lead to a “false positive,” i.e., the invalid acceptance of V˙O2peak as V˙O2max (30). Nonetheless, in CHF the end-exercise RERpeak has become the most commonly used secondary criterion to validate maximal effort and thus “confirm” V˙O2max (12, 21, 29, with a range of different “cut-off” values suggested: >1.00 (12); >1.05 (21); ≥1.10 (2, 3, 22, 29). However, interpretation of RERpeak is complicated by the fact that a progressive exercise test is often delivered at a predetermined incrementation rate—a factor that interacts with the absolute lactate threshold (LT) and V˙O2max to influence the rate of blood lactate accumulation and therefore, ventilation (Ve), CO2 output (V˙CO2), and RERpeak attained at end exercise (6, 24). As such, RERpeak is a poorly sensitive criterion for V˙O2max confirmation.

An alternative exercise testing protocol has been proposed (31) that allows attainment of V˙O2max to be detected without the need for secondary criteria. This ramp-incremental (RI) step-exercise (SE) (or RISE) (31) test incorporates a verification phase (19, 23) to determine whether V˙O2max has, or has not, been attained during a standard incremental test. Importantly the RISE test provides a within-patient verification by direct comparison of two discrete V˙O2peak values generated from two different work rates, meeting the traditional criterion for V˙O2max measurement (14). The outcome is, therefore,
patient specific and does not rely on the application of broad cut-off criteria to all participants. This approach has been used successfully in healthy participants [both children (32) and adults (9, 23, 31)], in children with spina bifida (10) and adolescents with cystic fibrosis (39), but not yet in CHF patients.

We therefore aimed to determine whether the RISE test could provide a more robust method to determine V\textsubscript{O}\textsubscript{2}\text{max} in patients with CHF than the traditional secondary criterion (15). We hypothesized that 1) RER\textsubscript{peak} would be sensitive to ramp rate in CHF patients, and thus provide a poor criterion for maximal effort and V\textsubscript{O}\textsubscript{2}\text{max} detection; and 2) the RISE test would be well tolerated by CHF patients, thus allowing sensitive V\textsubscript{O}\textsubscript{2}\text{max} detection independent of ramp rate or secondary criteria.

**METHODS**

**Patients.** Twenty-four male and consecutive volunteers with symptomatic but stable CHF (Table 1), due to left ventricular systolic dysfunction and no recent (<3 mo) changes in medical therapy, provided written informed consent to participate in this study. All patients had previously undergone a clinically indicated cardiopulmonary exercise test and were approached at the end of the visit unless they were significantly limited by arthritis or severe chronic airways disease. We also excluded a total of 7 patients on the basis of either ongoing ischemia or dysrhythmias (n = 3) or a recent V\textsubscript{O}\textsubscript{2}\text{peak} > 20 ml·kg\textsuperscript{-1}·min\textsuperscript{-1} (n = 4). The latter criterion was used because patients with a V\textsubscript{O}\textsubscript{2}\text{peak} > 20 ml·kg\textsuperscript{-1}·min\textsuperscript{-1} generally have significant improvements in prognosis and only mild exercise limitation (20, 25); the present study therefore aimed to determine the efficacy of the RISE test in patients with moderate to severe exercise limitation. The investigation was approved by the Leeds West Local Research Ethics Committee, in accordance with the Declaration of Helsinki.

**Equipment and measurements.** Exercise tests were performed on an electromagnetically braked cycle ergometer (Excalibur Sport, Lode BV, Groningen, The Netherlands). Power output and cadence were recorded from the ergometer via digital data transformation (PowerLab 8/30, ADI Instruments, Chalgrove, UK). A 12-lead electrocardiogram was monitored throughout each test, and heart rate (HR) was measured beat-by-beat from the R-R interval (ECG; Burdick Quest, Cardiovascular, Sale, UK). Arterial O2 saturation (SpO\textsubscript{2}) was measured from the earlobe by pulse oximetry (Biox 3745, Ohmeda, Louisville, KY), and blood pressure by auscultation using a sphygmomanometer. Ratings of perceived exertion (difficulty of breathing and leg discomfort) were recorded by patients on a visual analog scale (0–100%) during baseline cycling, every 2 min during ramp-incremental exercise, and immediately following volitional exhaustion.

Respired gas was sampled continuously from a mouthpiece at 0.5 ml/s and analyzed at 50 Hz for relative concentrations of N\textsubscript{2}, O\textsubscript{2}, and CO\textsubscript{2}. Expiratory and inspiratory flows and volumes were measured by a low-dead-space (90 ml), low-resistance (<0.65 cmH\textsubscript{2}O at 8.5 l/s) turbine volume transducer. Gas concentrations and volume signals were digitized every 20 ms and time aligned for breath-by-breath calculation of pulmonary gas exchange (4) (V\textsubscript{O}\text{2}, V\textsubscript{CO}\text{2}, RER) and ventilatory variables (Ve; tidal volume, V\textr; breathing frequency, B\textf) (MSX, nSpire Health, Hertford, UK). The system was calibrated before (and verified following) each experiment using precision-analyzed gas mixtures and a 3-liter syringe (Hans Rudolph, Shawnee, KS). Noninvasive estimation of LT was made independently by three experienced researchers using the V-slope method and corroborated in the profiles of the end-tidal partial pressures of O2 and CO2, the ventilatory equivalents for V\textsubscript{O}\text{2} and V\textsubscript{CO}\text{2}, and RER (38).

**Exercise protocols.** Following familiarization, patients (n = 24) completed a single visit symptom-limited RISE-95 cycle ergometry test (31) to the limit of tolerance in the format: RI (ramp-incremental; 4–18 W/min); 5 min recovery (10 W); SE-95 (step-exercise from 10 W to 95% of the peak work rate achieved in the RI). Of this cohort, 18 patients also performed a RISE-95 test with either a fast (10–30 W/min) or slow (3–8 W/min) RI phase. The fast, medium, and slow ramp tests were performed over consecutive weeks (with 7 days between each visit) in a randomized order and at a similar time of day. The incremental rate was individually selected for each patient to induce volitional intolerance in approximately 5, 10, and 15 min, respectively. The different ramp durations were determined by initially estimating each patient’s V\textsubscript{O}\textsubscript{2}\text{peak} as calculated from prediction equations based on sex, age, height, and body mass (26) or from a previously performed clinically indicated exercise test performed in the cardiology clinic), and then by assuming a V\textsubscript{O}\text{2}-to-work rate relationship of 10 ml·W\textsuperscript{-1}·min\textsuperscript{-1} (38). V\textsubscript{O}\textsubscript{2}\text{peak} estimates from these nomograms were then adjusted downward in line with disease severity and a ramp rate assigned. Each RI and SE phase was terminated when pedal cadence could not be maintained above ~50 rpm, and, on one occasion, a test was terminated due to the onset of runs of multifocal ectopic beats. Tests were preceded and followed by at least 4 min of baseline cycling at 10 W. Patients were advised to be postprandial (2–3 h) and refrain from strenuous activity (24 h), caffeine (3 h) and alcohol consumption (48 h) prior to testing.

**Data analysis.** Breath-by-breath gas exchange and ventilatory responses were edited in the V\textsubscript{O}\text{2} domain, to exclude occasional breaths that lay outside four SDs of the local mean, resulting from sighs, coughs, swallows, etc. (18). Peak pulmonary and ventilatory variables were measured from each phase of the RISE-95 test were then determined with the aim of providing a measurement sensitivity of 50 ml/min in the V\textsubscript{O}\text{2} domain. Sensitivity was identified using a power analysis based on the widest breath-by-breath SD found in all participants to our laboratories over 3 years (150 ml/min) (see also Ref. 18). A power analysis therefore suggests that a sample size of 12 breaths is sufficient to detect a 50 ml/min difference in V\textsubscript{O}\text{2}, even in patients with the widest breath-by-breath fluctuations. This number of breaths also provides a sufficiently short duration (the average in this study was 19 ± 4 s during both exercise bouts) relative to the different dynamics of the RI and SE phases of the test to allow an appropriate comparison to be made. V\textsubscript{O}\textsubscript{2}\text{peak} was defined as the greatest V\textsubscript{O}\text{2} occurring during each

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>64 ± 11</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172 ± 7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>88 ± 16</td>
</tr>
<tr>
<td>Etiology of CHF</td>
<td></td>
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<tr>
<td>IHD</td>
<td>16</td>
</tr>
<tr>
<td>DCM</td>
<td>8</td>
</tr>
<tr>
<td>NYHA functional class; I/II/III</td>
<td>4/19/1</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>31 ± 8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7</td>
</tr>
<tr>
<td>Cardiac resynchronization device</td>
<td>9</td>
</tr>
<tr>
<td>Drug Therapy</td>
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<tr>
<td>ACE inhibitor</td>
<td>22</td>
</tr>
<tr>
<td>Aspirin</td>
<td>17</td>
</tr>
<tr>
<td>ß-Blocker</td>
<td>22</td>
</tr>
<tr>
<td>Digoxin</td>
<td>4</td>
</tr>
<tr>
<td>Furosemide</td>
<td>19</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>18</td>
</tr>
<tr>
<td>Statin</td>
<td>18</td>
</tr>
</tbody>
</table>

Data are means ± SD; n = number of patients. CHF, chronic heart failure; ACE, angiotensin-converting enzyme; DCM, dilated cardiomyopathy; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
**RESULTS**

### Table 2. Responses of CHF patients to ramp-incremental (RI) exercise performing fast, medium, or slow increases in work rate

<table>
<thead>
<tr>
<th>Ramp Rate</th>
<th>Fast</th>
<th>Medium</th>
<th>Slow</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Ramp rate, W/min</td>
<td>19 ± 6*</td>
<td>9 ± 4*</td>
<td>5 ± 1*</td>
</tr>
<tr>
<td>Duration, min</td>
<td>5.8 ± 0.5*</td>
<td>9.8 ± 1.4*</td>
<td>15.1 ± 1.9*</td>
</tr>
<tr>
<td>Peak work rate, W</td>
<td>117 ± 33*</td>
<td>93 ± 29*</td>
<td>81 ± 26*</td>
</tr>
<tr>
<td>V̇O₂peak, ml·kg⁻¹·min⁻¹</td>
<td>14.6 ± 2.4</td>
<td>14.2 ± 2.6</td>
<td>14.3 ± 3.1</td>
</tr>
<tr>
<td>V̇O₂peak, l/min</td>
<td>1.30 ± 0.23</td>
<td>1.27 ± 0.26</td>
<td>1.28 ± 0.29</td>
</tr>
<tr>
<td>V̇CO₂peak, l/min</td>
<td>1.58 ± 0.31*</td>
<td>1.47 ± 0.34†</td>
<td>1.40 ± 0.37†</td>
</tr>
<tr>
<td>RERpeak</td>
<td>1.21 ± 0.07*</td>
<td>1.15 ± 0.07*</td>
<td>1.09 ± 0.06*</td>
</tr>
<tr>
<td>V̇Epeak, l/min</td>
<td>63 ± 14*</td>
<td>59 ± 15†</td>
<td>56 ± 18†</td>
</tr>
<tr>
<td>B̆, breaths/min</td>
<td>37 ± 7</td>
<td>37 ± 9</td>
<td>35 ± 7</td>
</tr>
<tr>
<td>LT, ml·kg⁻¹·min⁻¹</td>
<td>10.1 ± 1.6</td>
<td>9.7 ± 1.6†</td>
<td>9.7 ± 1.5</td>
</tr>
<tr>
<td>LT, l/min</td>
<td>0.90 ± 0.15</td>
<td>0.87 ± 0.14†</td>
<td>0.87 ± 0.16</td>
</tr>
<tr>
<td>Resting HR, beats/min</td>
<td>70 ± 11</td>
<td>71 ± 13</td>
<td>71 ± 11</td>
</tr>
<tr>
<td>Peak HR, beats/min</td>
<td>123 ± 15</td>
<td>115 ± 22</td>
<td>115 ± 24</td>
</tr>
<tr>
<td>V̇E/V̇CO₂ at LT</td>
<td>36.1 ± 3.9</td>
<td>35.5 ± 3.7</td>
<td>35.9 ± 4.7</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>96 ± 4</td>
<td>95 ± 5</td>
<td>96 ± 3</td>
</tr>
<tr>
<td>Oxygen pulse, ml·beat</td>
<td>10.8 ± 1.8</td>
<td>11.2 ± 2.3</td>
<td>11.3 ± 2.2</td>
</tr>
</tbody>
</table>

Data are means ± SD. V̇O₂, pulmonary oxygen uptake; V̇CO₂, pulmonary carbon dioxide output; RER, respiratory exchange ratio; V̇E, minute ventilation; LT, lactate threshold; HR, heart rate; SpO₂, arterial oxygen saturation, B̆, breathing frequency. *P < 0.01 vs. all other ramp rates; †P < 0.01 vs. fast ramp rate.

### Statistical analysis.

V̇O₂peak values for RI and SE were compared in each patient by unpaired t-test. Unpaired comparisons were made between the 12-breath clusters at V̇O₂peak in the RI and SE phases because the order of appearance in V̇O₂ values is not paired, even though the comparison is within a patient. V̇O₂max and its individual 95% confidence interval (CI₉₅) (i.e., an individualized measurement sensitivity) was confirmed when the RI and SE V̇O₂peak values did not differ (P > 0.05). Where differences occurred (P < 0.05), the greater of the two V̇O₂peak values was reported (with its associated CI₉₅). This analysis resulted in two patient groups being identified, those in whom V̇O₂max was confirmed and those in whom a V̇O₂peak was attained.

Following this, therefore, paired t-tests were used for within-group comparisons of variables between RI and SE, while unpaired t-tests were used to compare variables between the two patient groups. Repeated-measures ANOVA was used to compare variables between different ramp rates. Data are presented as means ± SD. All analyses were completed using the Statistical Package for the Social Sciences (SPSS v.16.0, SPSS, Chicago, IL), and significance was accepted at P < 0.05.

### Influence of ramp rate on V̇O₂peak and RER.

The responses to fast, medium, and slow RI phases are summarized in Table 2. The V̇O₂ and RER profile for a representative patient and the group mean are shown in Fig. 1. The rate (and duration) of the three different RI phases were significantly (P = 0.001) different from each other: fast RI, 19 ± 6 W/min (6 ± 1 min); medium RI, 9 ± 4 W/min (10 ± 1 min); slow RI, 5 ± 1 W/min (15 ± 2 min). There was no effect of ramp rate on V̇O₂peak (average: 14.4 ± 2.6 ml·kg⁻¹·min⁻¹; P = 0.476 between ramp...
rates; \( n = 18 \); Table 2; Fig. 1, A and C), but RER_{peak} was correlated with ramp rate such that faster ramp rates resulted in significantly greater RER_{peak} values (\( P = 0.001; R^2 = 0.49 \); Table 2; Fig. 1, B and D), averaging 1.21 ± 0.1 (fast RI); 1.15 ± 0.1 (medium RI); and 1.09 ± 0.1 (slow RI). The number of patients who achieved an RER ± 1.10 i.e., a common threshold used to confirm maximal effort in CHF and thus VO_{2max} (2, 3, 22, 29) was 18, 14, and 7 for the fast, medium, and slow ramp rates, respectively.

**Confirming VO_{2max} using the RISE-95 test.** Patient responses (\( n = 24 \)) to the RISE-95 test are summarized in Table 3. In only 1 of the 24 tests was the SE phase not performed at the patient’s request. The average duration of the RI and SE phases were 10 ± 2 and 2 ± 1 min, respectively (\( P = 0.001 \)). Despite the peak work rate in RI being 5% greater than in SE (93 ± 31 vs. 89 ± 30 W; \( P = 0.001 \)), group VO_{2peak} was similar between RI and SE: 14.5 ± 3.0 vs. 14.7 ± 3.1 ml·kg^{-1}·min^{-1} (\( P = 0.407 \)). This was also the case when fast or slow ramps were used (\( n = 18 \)). While these group responses were not different, importantly a within-subject comparison of VO_{2peak} in RI and SE phases revealed that VO_{2max} was confirmed in 14 of 24 patients (Table 3; Figs. 2A and 3) and without the need for secondary criteria. The CI_{95} for VO_{2max} estimation averaged 1.4 ± 0.8 ml·kg^{-1}·min^{-1} (range 0.6–3.5 ml·kg^{-1}·min^{-1}). In these 14 patients RER_{peak} in RI averaged 1.15 ± 0.08 (range 1.01–1.31; Table 3). For the other 10 patients the VO_{2peak} values differed between the RI and SE phases (Table 3; Figs. 2B and 3), with VO_{2peak} in SE (14.8 ± 3.8 ml·kg^{-1}·min^{-1}) exceeding the value (\( P = 0.003 \)) attained in RI (13.5 ± 3.8 ml·kg^{-1}·min^{-1}) in 5 of these (Fig. 3). The CI_{95} for VO_{2peak} estimation averaged 0.9 ± 0.4 ml·kg^{-1}·min^{-1} (range 0.6–1.9 ml·kg^{-1}·min^{-1}). In these 10 patients RER_{peak} in RI was 1.14 ± 0.07 (range 1.05–1.26; Table 3). There were no differences in pathological, physiological (including VO_{2peak}), or clinical measures between the group of patients in whom a VO_{2max} was confirmed and those whom attained a VO_{2peak}. In addition, there was no difference (\( P = 0.835 \)) in VO_{2peak} in the RI and SE phases between the two groups (Table 3).

In the RISE-95 test the incidence of VO_{2max} detection was not significantly influenced by ramp rate. Eighteen patients completed the RISE-95 test with a fast, medium, and slow RI phase. In only 2 of the 36 tests was the SE phase contraindicated: one due to the patient’s reluctance to continue and the other at the physician’s discretion due to the onset of runs of multifocal ectopic beats. The VO_{2max} criterion was met in 11, 9, and 11 patients in the fast, medium, and slow ramps, respectively, without the need for secondary criteria and consistent with a high precision of the test. Using the traditional criterion for VO_{2max} detection however [RER_{peak} ≥ 1.10 (2, 3, 22, 29)], a VO_{2max} was confirmed in 18 of 24 patients at an average of 15.1 ± 2.6 ml·kg^{-1}·min^{-1}, providing a false positive in 7 (29%) and false negative in 3 (13%) cases. The RISE-95 test, on the other hand, confirmed VO_{2max} in 14 of 24 patients at an average of 15.3 ± 3.1 ml·kg^{-1}·min^{-1} without the incidence of false positive or negative and to a measurement sensitivity that was individualized for each patient (range 0.6–3.5 ml·kg^{-1}·min^{-1}).

**Symptoms limiting exercise.** During the RISE-95 test patient ratings at peak exercise for leg discomfort (82 ± 13%) were greater (\( P = 0.002 \)) than those for difficulty of breathing (66 ± 21%). There were no differences between the RI and SE ratings for difficulty of breathing (64 ± 21 vs. 69 ± 23%; \( P = 0.204 \)) or leg discomfort (80 ± 13 vs. 83 ± 13%; \( P = 0.595 \)), respectively.

**DISCUSSION**

The novel findings of this study for an exercise test incorporating ramp-incremental and a verification phase [i.e., a RISE-95 test (31)] were that 1) the test was well tolerated by patients with CHF; 2) the test provided criterion detection of VO_{2max} with a measurement sensitivity that was individualized for each patient; 3) VO_{2max} detection was independent of objective and subjective secondary measurements for confirmation of VO_{2max} attainment; 4) the test provided high precision in VO_{2max} identification over a range of ramp-incrementation rates; and 5) VO_{2max} was confirmed in only 60% of all patients who either confirmed (\( n = 14 \)) or failed to confirm (\( n = 10 \)) maximal oxygen uptake (VO_{2max}).

**Table 3. Cardiopulmonary responses to the ramp-incremental (RI) and step-exercise (SE) phases of the RISE-95 test in CHF patients who either confirmed (\( n = 14 \)) or failed to confirm (\( n = 10 \)) maximal oxygen uptake (VO_{2max}).**

<table>
<thead>
<tr>
<th>VO_{2max}</th>
<th>Confirmed</th>
<th>Not confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>RI</td>
<td>SE</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Ramp rate, W/min</td>
<td>9 ± 4</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>Duration, min</td>
<td>10.4 ± 2.4</td>
<td>2.9 ± 0.4*</td>
</tr>
<tr>
<td>Peak work rate, W</td>
<td>97 ± 31</td>
<td>92 ± 29*</td>
</tr>
<tr>
<td>VO_{2peak}, ml·kg^{-1}·min^{-1}</td>
<td>15.1 ± 3.0</td>
<td>15.2 ± 3.1</td>
</tr>
<tr>
<td>VO_{2peak}, l/min</td>
<td>1.30 ± 0.36</td>
<td>1.31 ± 0.36</td>
</tr>
<tr>
<td>VCO_{2peak}, l/min</td>
<td>1.51 ± 0.44</td>
<td>1.38 ± 0.40*</td>
</tr>
<tr>
<td>RER_{peak}</td>
<td>1.15 ± 0.08</td>
<td>1.05 ± 0.07*</td>
</tr>
<tr>
<td>V_{Epeak}, l/min</td>
<td>65 ± 17</td>
<td>66 ± 19</td>
</tr>
<tr>
<td>B_{R}, breaths/min</td>
<td>39 ± 10</td>
<td>41 ± 14</td>
</tr>
<tr>
<td>LT, ml·kg^{-1}·min^{-1}</td>
<td>10.0 ± 1.5</td>
<td>9.6 ± 1.9</td>
</tr>
<tr>
<td>LT, l/min</td>
<td>0.86 ± 0.16</td>
<td>0.85 ± 0.19</td>
</tr>
<tr>
<td>Baseline HR, beats/min</td>
<td>82 ± 20</td>
<td>94 ± 25*</td>
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<tr>
<td>Peak HR, beats/min</td>
<td>119 ± 26</td>
<td>118 ± 27</td>
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<tr>
<td>V_{E} / V_{CO2} at LT</td>
<td>37.6 ± 7.0</td>
<td>37.7 ± 9.5</td>
</tr>
<tr>
<td>SpO_{2}, %</td>
<td>96 ± 3</td>
<td>96 ± 2</td>
</tr>
<tr>
<td>Oxygen pulse, ml/beat</td>
<td>11.1 ± 2.7</td>
<td>11.3 ± 2.8</td>
</tr>
</tbody>
</table>

Data are means ± SD. Of note, one patient did not perform the step exercise (SE) phase. *\( P < 0.01 \) vs. ramp-incremental (RI) phase within subjects.
tests by CHF patients, despite group comparisons suggesting 
\( \dot{V}O_{2\text{max}} \) attainment in all. In addition, these data confirm that 
\( RER_{\text{peak}} \) is influenced by ramp rate during an incremental 
exercise test in CHF patients (6, 24), and that its use provides 
a false positive or negative for \( \dot{V}O_{2\text{max}} \) detection in up to 
40% of cases. We therefore recommend that the use of \( RER_{\text{peak}} \) as 
a measure of good effort (and hence \( \dot{V}O_{2\text{max}} \) corroboration) be 
viewed with extreme caution. As an alternative, the present 
data provide evidence to support the use of the RISE-95 test to 
accurately and reliably determine (or refute) \( \dot{V}O_{2\text{max}} \) along with 
a measurement sensitivity (CI 95) that is specific for each 
individual. The information provided by the RISE-95 test 
[which includes the \( \dot{V}O_{2\text{max}} \) criterion together with other prog-
nostic indicators such as \( V_{E}/V_{CO_{2}} \) and LT (33)] could therefore be beneficial in directing assessment and treatment in CHF 
patients.

**Influence of ramp rate on \( RER \).** The \( \dot{V}O_{2\text{peak}} \) at the limit of 
tolerance is a powerful diagnostic measure in CHF and provides 
key information on severity, prognosis, and the need for 
cardiac transplantation (20). However \( \dot{V}O_{2\text{peak}} \) is effort depen-
dent, meaning that a low value may not solely reflect the 
attainment of the physiological limit of \( O_{2} \). Conversely,

\( \dot{V}O_{2\max} \) is difficult to determine during standard incremental 
protocols because of the poor incidence (or sensitivity for 
detecting) a plateau in the dynamic \( VO_{2} \) profile (9, 31). For this 
reason a range of measurements corroborating maximal effort 
are suggested (15, 22), and of these the criterion that \( RER_{\text{peak}} \) 
exceeds a specific threshold value is the most common. For 
CHF patients \( RER_{\text{peak}} \) values > 1.00 (12), > 1.05 (21), or \( \geq \) 
1.10 (2, 3, 22, 29) have been recommended. However, and in 
contrast to recommended CHF guidelines (2, 3, 12, 22, 29), our 
findings suggest that the \( RER_{\text{peak}} \) is inappropriate for confirm-
ing maximal effort and \( \dot{V}O_{2\max} \).

This finding is likely due to the dynamics of \( VCO_{2} \) and its 
relation with the kinetics of \( CO_{2} \) storage and production. The 
\( CO_{2} \) evolved at the lung preceding and during peak exercise is 
derived from three sources: 1) metabolically produced \( CO_{2} \); 
2) additional \( CO_{2} \) derived from the buffering of \( H^{+} \) associated 
with the increase in blood and muscle [lactate]; and 3) compensatory 
hyperventilation in response to the metabolic acidosis reducing 
\( CO_{2} \) stores in the lung and other tissues (40). The faster ramp rates are suggested to induce a more rapid rate of 
[lactate] production, which in turn results in a greater rate of 
\( CO_{2} \) to be produced at the lung (40), leading to higher values

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**Fig. 2.** Breath-by-breath pulmonary oxygen uptake (\( VO_{2} \)) dynamics in two 
CHF patients in response to the ramp-incremental (RI) step-exercise (SE) at 
95% peak RI work rate (i.e., RISE-95) test. In the patients presented, one 
confirmed maximal oxygen uptake (\( \dot{V}O_{2\max} \); A), while the other did not 
(\( \dot{V}O_{2\text{peak}} \); B). Our within-patient analysis confirmed \( \dot{V}O_{2\max} \) in patients by 
statistically comparing the highest 12 breaths during exercise in the RI and SE 
phases, with values of \( P > 0.05 \) confirming \( \dot{V}O_{2\max} \). Dotted lines are presented 
to highlight the differences in the values of \( \dot{V}O_{2\text{peak}} \) between the RI and SE 
phases. \( * \) \( P < 0.05 \).

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**Fig. 3.** Relationship (A) and Bland-Altman plot (± SD) of the mean difference 
(\( \Delta \) ) (B) between the peak pulmonary oxygen uptake (\( \dot{V}O_{2\text{peak}} \)) achieved during 
the ramp-incremental (RI) and step-exercise (SE) (RISE-95) test in CHF 
patients who did (\( n = 14; \) • ) or did not (\( n = 9; \) ○) confirm maximal oxygen 
uptake (\( \dot{V}O_{2\max} \)). Of note, 1 of the 24 patients elected not to perform the SE 
bout.
of \( RER_{peak} \). This sensitivity of \( RER_{peak} \) to testing protocol is consistent with previous findings in healthy people (6) and CHF patients (24) (although see Ref. 1), and perhaps helps to explain why the use of \( RER_{peak} \geq 1.10 \) led to a false positive or negative for \( VO_{2max} \) detection in \(-40\%\) of our patients.

Confirming \( VO_{2max} \) within CHF patients. The maximum rate of \( O_2 \) delivery and utilization [\( VO_{2max} (37) \)] is regarded as the gold standard measure of aerobic capacity and integrated neuromuscular-cardiopulmonary functioning (29). Traditionally, \( VO_{2max} \) has been confirmed by an increase in work rate without an increase in \( VO_2 \), such that a “plateau” in \( VO_2 \) is exhibited when approaching the tolerable limit during incremental testing (14). This feature, however, is rarely discerned in CHF patients using modern ramp-incremental protocols (or indeed in healthy individuals, where plateau incidence is less than \(-50\%\) (9, 15, 31)). For this reason it was recommended (31) that RI exercise be followed by a verification phase (9, 19, 23) using a step increase to a work rate different from the peak work rate previously attained, thereby satisfying the plateau criterion for \( VO_{2max} \) where two different work rates are terminated at the same \( VO_2 \) (14). This approach has been shown to be effective in a range of healthy and patient groups (9, 10, 23, 31, 32, 39), but this study is the first demonstrating its efficacy in CHF patients.

An important addition of the present study is the application of a novel criterion to detect \( VO_{2max} \) and the associated \( CI_{O2} \) for each individual. Previous studies using a verification phase to determine \( VO_{2max} \) have typically focused on comparing group means; however, the clinical utility of this exercise test is its application to the individual rather than the group (27). Therefore the demonstration that \( VO_{2max} \) may be detected using a RISE-95 test within patients to a patient-specific confidence limit (and without the need for corroborating criteria) provides improved accuracy and precision to current techniques. Our findings are also consistent with the notion that peak exercise testing is safe and well tolerated by CHF patients (28), and even suggests repeated peak efforts may be safely performed after only a few minutes of active recovery. No adverse events occurred during 60 of the RISE-95 tests administered and the completion rate was high: the SE phase was completed in 57 of the 60 tests administered.

In the present study we defined \( VO_{2peak} \) attained in each phase of the RISE-95 test as the highest mean \( VO_2 \) value achieved in 12 consecutive breaths during exercise. It is well recognized, especially in CHF patients (8), that \( VO_2 \) may increase after exercise cessation. Although the actual mechanisms for this increase are not well defined (and may vary between individuals), there is a series of events that may contribute to the increase in \( VO_2 \) after cessation in CHF. An acute increase in stroke volume during active recovery from peak RI [consistent with the observed increase in \( O_2 \) pulse in some CHF patients (38)] may occur in CHF patients due to an abrupt reduction in thoracic pressure and end-expiratory lung volume, together with a relative maintenance of peak HR and muscle pump in active recovery. This can result in an acute increase in cardiac output (36) and therefore in \( VO_2 \) measured across the lung, which may be exacerbated by reduced lung \( O_2 \) stores (from a reduced end-expiratory lung volume) when \( VO_2 \) is measured at the mouth (41). In addition, the long limb-to-lung transit time at peak RI, associated with low absolute cardiac output in CHF (35), can result in the arteriovenous \( O_2 \) concentration difference across the lung continuing to rise for \(-15\sim-20\) s after exercise cessation, despite the dramatic reduction in power output. This effect is thought to be less at a greater absolute \( VO_2 \) and cardiac output values (i.e., in healthy or endurance-trained subjects) where the rate of rise in arteriovenous \( O_2 \) concentration difference across the legs at the end of the RI phase is less pronounced than in CHF (17, 35). Consistent with this we found a modest \( 40 \pm 32 \) ml/min increase in pulmonary \( VO_2 \) in \(-30\%\) of our patients in the present study. However, in line with previous suggestions (7) we reported the \( VO_{2peak} \) and \( VO_{2max} \) values as those achieved during the exercise (rather than in recovery) as this reflects the functional physiological limitation of the task being performed.

An interesting finding of the present investigation was that 5 of 24 patients (\(-20\%\)) achieved a statistically greater \( VO_{2peak} \) in the SE phase of the RISE-95 test (Fig. 3). This is very rarely seen in healthy subjects (Refs. 9, 31; unpublished observations from our laboratory suggest an incidence of \(-3\%\)) and suggests CHF patients may have a cardiac and/or metabolic reserve (11, 16), with the alleviation of some limit to cardiac output or muscle \( O_2 \) extraction between RI and SE allowing \( VO_{2peak} \) to be greater in SE. The mechanism underlying the increase in \( VO_{2peak} \) in these 5 patients is unclear, as no clinical or physiological differences were detected. An increase in muscle recruitment (16) between RI and SE seems unlikely considering the exercise modality was identical and work rate was \(-5\%\) lower during the SE bout. Moreover, increased cardiac output between bouts also seems unlikely considering long-term exercise training fails to significantly improve hemodynamic measurements in CHF patients (34). It is possible that patients’ symptoms may have been attenuated between exercise phases allowing an increase in \( VO_{2peak} \); however, symptoms at peak exercise were also similar between bouts. Therefore, the increase in \( VO_{2peak} \) may relate to the residual effects of the previous exercise bout. In CHF patients (5) and healthy older adults (13), warm-up exercise can speed \( VO_2 \) kinetics while also increasing microvascular \( O_2 \) delivery and intramuscular aerobic enzyme activity. Whether these mechanisms can increase the \( VO_{2peak} \) in CHF remains to be determined. Whatever the etiology of this mechanism(s), however, targeting it could provide a beneficial avenue for therapeutic interventions to increase aerobic capacity and thus benefit the activities of daily living in CHF patients.

Clinical implications. The present data suggest that \( RER_{peak} \) as a measure of maximal effort in cardiopulmonary exercise testing be abandoned, and the RISE-95 test is recommended for \( VO_{2max} \) confirmation. This may have important consequences for current clinical guidelines. For example, out of all tests the increase in \( VO_{2peak} \) between RI and SE phases led some patients (17%) to acutely increase Weber classification scores and other patients (38%) to cross thresholds of cardiac transplantation listing, either as an accepted indication \((n = 2; \leq 10 \mathrm{ml}\cdot\mathrm{kg}^{-1}\cdot\mathrm{min}^{-1})\) or a probable indication \((n = 4 \text{ for } \leq 14 \mathrm{ml}\cdot\mathrm{kg}^{-1}\cdot\mathrm{min}^{-1}; \text{ and } n = 3 \text{ for } \leq 12 \mathrm{ml}\cdot\mathrm{kg}^{-1}\cdot\mathrm{min}^{-1} \text{ in presence of } \beta\text{-blocker} \text{ therapy}) (20, 21). The significance of these findings cannot be directly assessed in this small cohort study, but there is a clear implication that patient stratification and treatment decisions may be affected by “underestimation” of \( VO_{2max} \). The practical application and statistical analysis for \( VO_{2max} \) confirmation using the RISE test is simple and therefore could be easily incorporated into computational algo
rithms in commercial “metabolic cart” software to provide an objective assessment of attainment (or not) of \( \text{VO}_{2\text{max}} \). This would provide an increased accuracy and precision for patient stratification or identification of patients with poor motivation or a poor quality test for other reasons (whose exercise test outcomes could then be interpreted with the appropriate caveat). The RISE-95 test could also increase cost effectiveness of treatment strategies in CHF by reducing the incidence of misdirected therapeutic consequences that are, in part, due to an underestimation of maximal responses in cardiopulmonary exercise testing.

Whether \( \text{VO}_{2\text{max}} \) detection by the RISE-95 test could provide a stronger prognostic or diagnostic tool than \( \text{VO}_{2\text{peak}} \) (20), or other prognostic markers (33), is currently unclear. For example, a recent comprehensive review suggests that \( \text{VE}/\text{VCO}_{2} \) (a noninvasive proxy for abnormalities in pulmonary ventilation-to-perfusion inequalities) provides a stronger prognostic index than \( \text{VO}_{2\text{peak}} \) (33). Whether the \( \text{VO}_{2\text{peak}}/\text{VO}_{2\text{max}} \) value obtained in the RISE-95 test would increase the prognostic value of \( \text{VO}_{2} \) in this regard, however, remains to be determined, because previous tests may have underestimated the \( \text{VO}_{2\text{max}} \) in a significant proportion of cases. Considering all tests in the present study, this “underestimation” exceeded 0.6 ml·min\(^{-1}\)·kg\(^{-1}\) in about 60% of patients, a value that was associated with an 11% reduction in all-cause mortality and hospitalizations in a recent large multicenter clinical trial of exercise training in CHF (28). Moreover, seven patients (~30%) in the present study increased \( \text{VO}_{2\text{peak}} \) between RI and SE by more than the generally accepted minimal important clinical difference of 10% (28). Nevertheless, as both \( \text{VE}/\text{VCO}_{2} \) (determined submaximally) and \( \text{VO}_{2\text{max}} \) are independently and objectively determined in the RISE-95 test, a prognostic test that incorporates both measurements (and possibly others, e.g., estimated LT) may provide the strongest predictive power offered by cardiopulmonary exercise testing (33). Our findings also suggest that the RISE-95 test may have important implications for current equations predicting patients’ \( \text{VO}_{2\text{peak}} \) (26, 38). However, these data were collected from a relatively small and exclusively male patient group, and a wider study with long-term follow-up is needed to clarify any predictive or prognostic value of the test and to extend the present findings to the wider CHF population.

Conclusions. The present study has found that ramp-incrementation rate significantly influences the RER\(_{\text{peak}}\) during peak exercise testing in patients with CHF. These data suggest, therefore, that the use of RER\(_{\text{peak}}\) as a measure of good effort (and hence \( \text{VO}_{2\text{max}} \) corroboration) be abandoned. In contrast, the present data provide evidence to support the use of the RISE-95 test (31). This protocol was well tolerated by CHF patients, able to detect \( \text{VO}_{2\text{max}} \) with a measurement sensitivity (Cl\(_{\text{est}}\)) specific for each patient, independent of additional objective or subjective secondary measurements used to confirm \( \text{VO}_{2\text{max}} \) and provided high precision over a range of incrementation rates. Together these data suggest that the RISE-95 test should be included in standard clinical exercise testing procedures.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS


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