Effect of Acute β-blocker Withholding on Ventilatory Efficiency in Patients With Advanced Chronic Heart Failure

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ABSTRACT

Background: This is the first study to examine the effect of acute (24-hour) β-blocker withholding on ventilatory efficiency in patients with advanced chronic heart failure (CHF) during maximal incremental treadmill cardiopulmonary exercise test.

Methods and Results: Seventeen CHF patients were studied either 3 hours after administration of β-blocker (BBON) or 27 hours after the last β-blocker ingestion (BBOFF). The ventilatory efficiency was measured via the slope of the linear relationship between ventilation (V'E) and carbon dioxide production (V'CO2) (i.e., V'E/V'CO2 slope). Measurements were also made at rest, anaerobic threshold (AT), maximal end-tidal pressure for carbon dioxide (PETCO2max), respiratory compensation point (RC), and peak exercise. Compared with BBOFF, the V'E/V'CO2 slope was significantly increased during BBON (30.8 ± 7.4 vs. 29.1 ± 5.4, P = .04). At peak exercise, oxygen uptake (VO2, 16.0 ± 2.7 vs. 15.6 ± 2.8 mL·kg·min) and V'CO2 (1458 ± 459 vs. 1414 ± 429 mL·min) were not different between the 2 conditions, whereas V'E was higher during BBOFF (49.5 ± 10.7 vs. 46.1 ± 9.6 L·min, P = .04). No differences were noted at AT and RC in V'CO2, V'E, V'VE/V'CO2, and PETCO2 ratios during the 2 conditions. At PETCO2max, used to noninvasively estimate the CO2 set point, V'E was higher (33.9 ± 7.6 vs. 31.7 ± 7.3 L·min, P = .002) and PETCO2 was lower (37.4 ± 4.8 vs. 38.5 ± 4.0 mm Hg, P = .03), whereas V'CO2 was unchanged (1079 ± 340 vs. 1050 ± 322 mL·min) during BBOFF.

Conclusion: Acute β-blocker withholding resulted in decreased ventilatory efficiency mostly from an increase of V'CO2-independent regulation of V'E and less likely from a change in ventilation/perfusion mismatching. (J Cardiac Fail 2010;16:548–555)

Key Words: β-blocker, chronic heart failure, ventilatory efficiency, exercise capacity.

The relationship between ventilation and carbon dioxide production (i.e., the V'E/V'CO2 slope) is a measure of ventilatory efficiency and can be used to identify an abnormal ventilatory response to exercise.1,2 Patients with chronic heart failure (CHF) often present with an impaired ventilatory response to exercise.2–4 In CHF, the V'E/V'CO2 slope is a strong prognostic marker independent from other exercise related heart failure prognostic markers such as peak oxygen uptake (VO2).3,5

Long-term treatment with β-blockers has been shown to reduce the V'E/V'CO2 slope in patients with CHF during exercise.6,7 Although the precise mechanism(s) underlying this improvement remain to be fully elucidated, amelioration of ventilation/perfusion mismatching,6 as well as regulation of the partial arterial pressure of carbon dioxide (Paco2) set point (which is in part controlled by sympathetic nervous system activity),7,8 have been advocated as potential contributory factors.5,7

Of note, acute hemodynamic effects of β-blocking are often deleterious with a fall in ejection fraction and rise in peripheral vascular resistance in patients with CHF,9,10 whereas the chronic effect of changes in β-receptor density11–14 may best explain the observed benefits on cardiac structure and clinical outcomes.15,16 Indeed, β-blockers exert many acute and chronic effects on both
cardiac and noncardiac receptors including ventricular β-adrenoceptors,12–14 as well as chemo-, metabo-, and ergo-receptors in the peripheral muscles indirectly via sympathetic system activation.6–8

In principal, the improved ventilatory efficiency seen after long-term treatment could be due to acute as well as chronic effects of β-blockers. Accordingly, we examined the effect of 24-hour β-blocker withholding on ventilatory efficiency in patients with advanced CHF during maximal incremental treadmill cardiopulmonary exercise test and compared our data on acute β-blocker withholding with historical published data on chronic (2-month) β-blocker withholding from Agostoni and coworkers7 to find out whether a unified mechanism could explain the effect of acute and chronic β-blocker withholding on ventilatory efficiency in CHF patients.

Methods

Subjects

All patients with advanced systolic CHF, in New York Heart Association Class II-IV, on stable medical therapy including β-blockers for at least 3 months referred for cardiopulmonary exercise tolerance testing (CPET) were screened for participation in the study from March 2008 through December 2008. Patients with atrial fibrillation, inability to exercise, hospital admission for heart failure, or acute coronary syndrome in the past 90 days or with symptoms of myocardial ischemia were excluded. Also excluded were patients with other medical conditions, such as respiratory diseases, primary pulmonary hypertension, or neuromuscular and orthopedic diseases, which could cause or contribute to exercise intolerance. The study was approved by the institutional review board of New York Presbyterian Hospital, Columbia University Medical Center. Informed consent was obtained from all participants.

Study Design

This was a randomized, parallel, crossover study. Each participant performed 2 CPETs at 10 am in the morning conducted 5 to 7 days apart. Subjects were instructed to either take β-blockers 3 hours before the visit or to withhold β-blockers following the 7 am dose on the preceding day. Accordingly, 1 test was conducted 3 hours after administration of β-blocker (BBON), whereas the other test was performed 27 hours after the last β-blocker ingestion (BBOFF). BBON and BBOFF visits were performed in random order to eliminate possible training effects. The investigator(s) responsible of performing CPET was not involved in the analysis of the results.

CPET

During each visit, patients underwent a symptom-limited incremental treadmill CPET. The work rate increased continuously as a ramp function by augmenting the speed and grade of the treadmill according to a modified Naughton protocol. Patients were instructed to exercise until the point of symptom limitation. Patients were strongly encouraged to perform a maximal test, but they determined when their symptoms were so severe that it was necessary to stop exercising. Resting heart rate (HR) was obtained after 30 minutes of rest in a quiet, temperature-controlled room. Electrocardiographic monitoring of HR, rhythm, and ST-segment changes were recorded continuously at rest and throughout exercise testing, whereas blood pressure (by indirect sphygmomanometry) was collected at rest, every 2 minutes during exercise, and upon completion of exercise. Cardiopulmonary and breathing pattern measurements were collected in a breath-by-breath fashion while subjects breathed through a mouthpiece with attached low-resistance flow transducer with nasal passages occluded by a nose clip using a Medgraphics metabolic cart (Medical Graphics Corporation St. Paul, MN). V̇E, V̇Ȯ2, V̇CȮ2, end-tidal oxygen and carbon dioxide partial pressure (PETO2 and PETCO2, respectively), tidal volume (VT), and respiratory frequency (RF) were calculated. Exercise variables were measured continuously and averaged over the last 20 seconds of each minute and at peak exercise, defined as the last 20 seconds of loaded exercise. The instruments were calibrated before every test and were corrected for humidity, room temperature, and barometric pressure, according to the manufacturer’s protocol. Peak V̇Ȯ2 (V̇Ȯ2peak) and peak V̇E (V̇Epeak) were defined, respectively, as the highest value of V̇Ȯ2 and V̇E that could be sustained for at least 20 seconds during the last stage of exercise when the respiratory exchange ratio (RER) was > 1.0. Metabolic and cardioventilatory variables were reported according to formulas as previously described.17

The anaerobic threshold (AT) was detected individually using the V-slope method and verified against other points; that is, the V̇Ȯ2 at which the ventilatory equivalent for oxygen (V̇E/V̇Ȯ2) begins to increase systematically without an increase in the ventilatory equivalent for carbon dioxide (V̇E/V̇CȮ2) and where ṖETO2 begins to increase without a decrease in ṖETCO2.18 The respiratory compensation point (RC) was calculated as the point where the slope of the V̇E/V̇CO2 relationship started to increase.18 The maximal ṖETCO2 was defined as the highest value of ṖETCO2 observed during exercise test, between the AT and the RC point, when ṖETCO2 remains constant.18 This was done to evaluate the CO2 set point, which can be noninvasively estimated by the ṖETCO2 during exercise before the metabolic compensation point is reached. Exercise capacity was assessed by measuring the V̇Ȯ2 at AT and peak. Mismatching of the heart and lungs was evaluated via the ventilatory efficiency measure V̇E/V̇CO2 slope (ie, the slope of the linear relationship between V̇E and V̇CO2 from 1 minute after the beginning of loaded exercise to the end of the isocapnic buffering period).18 Two blinded experienced readers independently interpreted each test, and the results were averaged.

For statistical analysis purposes, 5 main points were used for evaluation of exercise parameters: 1) pre-exercise rest (baseline), defined as the steady-state period after at least 3 minutes of breathing on the mouthpiece while being at rest before the start of exercise; 2) AT; 3) maximal ṖETCO2; 4) RC point; and 5) peak exercise.

Statistical Analysis

Results were expressed as means ± SD. A P < .05 level of statistical significance was used for all analyses. The current study’s group responses at different exercise level points during treadmill exercise (baseline, AT, RC, maximal ṖETCO2, and peak) were compared using paired t-tests with appropriate Bonferroni adjustments for multiple comparisons. Comparisons between data from the current study and those from Agostoni et al were made using unpaired t-tests. Repeated measurement analysis was not performed because we were interested in treatment effects at specific exercise points/levels rather than in interactions between treatment and time over the course of the exercise test. Pearson correlations were used to establish associations between dependent variables such as peak V̇E, V̇E/V̇CO2 slope and ratios, and relevant
independent variables, such as HR and rest-to-peak difference in HR (ΔHR) and any other measured cardiopulmonary variables.

Results

Cardiovascular Response to CPET

Differences in cardiovascular responses at rest and at peak exercise after BBOFF compared with BBON are shown in Table 2. Based on Weber classification of severity,19,20 1 patient presented with V'\text{O}_2 at AT > 14 mL·min⁻¹·kg⁻¹ and V'O_2 peak > 20 mL·min⁻¹·kg⁻¹ (Class A, little or no impairment), 9 patients with V'O_2 at AT falling between 11 and 14 mL·min⁻¹·kg⁻¹ and V'O_2 peak between 16 and 20 mL·min⁻¹·kg⁻¹ (Class B, mild-to-severe impairment), whereas 7 patients presented with V'O_2 at AT falling between 8 and 11 mL·min⁻¹·kg⁻¹ and V'O_2 peak between 10 and 16 mL·min⁻¹·kg⁻¹ (Class C, moderate-to-severe impairment) during BBOFF. BBOON did not affect exercise capacity; V'O_2 peak, V'O_2 at AT and time to exhaustion were unaffected by BBOON (Tables 2, 3). BBOFF patients presented at rest with higher HR, by 6 ± 6 beats/min (~8%, \( P = .0006 \)), compared with BBON patients, but with no difference in resting V'O_2 (Table 2). BBOFF patients stopped exercise at higher HR, by 9 ± 11 beats/min (~7-8%, \( P = .003 \)), but with no difference in peak V'O_2 (Table 2). HR and V'O_2 values at AT, maximal \( \text{PETCO}_2 \) and RC point after β-blockers withholding compared with BBON are shown in Table 3. Rest-to-peak changes in HR ranged from 50 ± 21 beats/min during BBOFF session to 47 ± 17 beats/min during BBON session.

Ventilatory Response to CPET

β-blocker withholding did not affect V'E at rest, nor at AT or at RC point (Tables 2, 3). At peak exercise, V'E was increased by 3.5 L/min (by 7%, \( P = .04 \)) in the presence of no differences in V'\text{CO}_2, V'T, and Rf after β-blocker withholding compared with BBON (Table 2). Rest-to-peak changes in V'E ranged from 39.2 ± 9.5 L/min during BBOFF session to 35.9 ± 9.3 L/min during BBON session. At maximal \( \text{PETCO}_2 \), which was observed between the AT and the RC point, V'E was 2.2 L/min higher (\( P = .002 \)) and \( \text{PETCO}_2 \) 1.1 mm Hg lower (\( P = .03 \)), whereas V'\text{CO}_2 was not significantly changed after β-blocker withholding (Table 3).

β-blocker withholding did not affect V'E/F'/\text{CO}_2 slope by ~5–6%, from the average value of 29.1 ± 5.4 to the average value of 30.8 ± 7.4 (\( P = .04 \)) (Fig. 1). Based on Arena ventilatory class (VC) system,21 9 patients presented with V'E/F'/\text{CO}_2 slope ≥29.9 (VC I), 6 patients with V'E/F'/\text{CO}_2 slope between 30.0 and 35.9 (VC II), 1 patient with V'E/F'/\text{CO}_2 slope between 36.0 and 44.9 (VC III), and 1 patient with V'E/F'/\text{CO}_2 slope ≥45.0 (VC IV) during BBOFF. During BBON, 11 patients showed a V'E/F'/\text{CO}_2 slope ≤29.9 (VC I), 4 patients a V'E/F'/\text{CO}_2 slope between 30.0 and 35.9 (VC II), 1 patient with V'E/F'/\text{CO}_2 slope between 36.0 and 44.9 (VC III), and 2 patients a V'E/F'/\text{CO}_2 slope between 36.0 and 44.9 (VC IV), whereas no one showed a V'E/F'/\text{CO}_2 slope ≥45.0 (VC IV).

The ventilatory equivalents for oxygen and carbon dioxide (V'E/\text{O}_2 and V'E/F'/\text{CO}_2, respectively) were not significantly different during BBOFF session compared with BBON session at rest and at peak exercise (Table 2), as well as at AT (V'E/\text{O}_2 = 30 ± 7 vs. 29 ± 5; V'E/F'/\text{CO}_2 = 32 ± 7 vs. 32 ± 5), and at RC point (V'E/\text{O}_2 = 34 ± 11 vs. 32 ± 7; V'E/F'/\text{CO}_2 = 33 ± 8 vs. 32 ± 6) (Table 3). No differences were also found in \( \text{PETCO}_2 \) and \( \text{PETCO}_2 \) values at the previously mentioned levels of exercise in both sessions. Both V'E/\text{O}_2 and V'E/F'/\text{CO}_2 ratios were ~2 units higher during BBOFF sessions at maximal \( \text{PETCO}_2 \) because of the higher V'E at this level of exercise (Table 3).

Correlates of Improvement

The difference (Δ) in peak HR between BBOFF and BBON, an indicator of sinoatrial β1-receptor blockade,22 did not correlate with the Δ in V'E/F'/\text{CO}_2 slope between BBOFF and BBON (\( r = -.027, P = .3 \)) (Fig. 2A), nor with the Δ in peak V'E between BBOFF and BBON (\( r = -.023, P = .4 \)) (Fig. 2B). The Δ peak HR did not correlate with Δ peak V'O_2 expressed either as mL/min (\( r = .25, P = .3 \)) or as mL·kg⁻¹·min (\( r = .31, P = .2 \)). The Δ peak V'E and Δ V'E/F'/\text{CO}_2 slope correlated both with Δ peak \( \text{PETCO}_2 \) (\( r = -.826, P = .00004 \) and \( r = -.791, P = .0002 \), respectively). Of note, the Δ V'E/F'/\text{CO}_2 slope also correlated with Δ maximal \( \text{PETCO}_2 \) (\( r = -.64, P = .007 \)), and Δ V'E measured at maximal \( \text{PETCO}_2 \) correlated with Δ maximal \( \text{PETCO}_2 \) (\( r = -.56, P = .03 \)) (Fig. 3A, B). The Δ V'E/F'/\text{CO}_2 slope did not correlate with Δ peak V'O_2, expressed either as mL/min (\( r = -.38, P = .1 \)) or as mL·kg⁻¹·min (\( r = -.46, P = .06 \)).

Comparison with Historical Controls

We decided to compare our data on acute β-blocker withholding with historical published data on chronic (2-month)
β-blocker withholding to find out whether a unified mechanism could explain the effect of acute and chronic β-blocker withholding on ventilatory efficiency in CHF patients.

We compared data of 14 of the 17 subjects of the present experiment who were on carvedilol with historical and previously published data of 8 CHF patients who were studied after chronic (2-month) β-blocker withholding by Agostoni and coworkers (Fig. 1, Group B, from reference 7). Indeed, we had access and reanalyzed the Agostoni et al data to evaluate only those patients who had prolonged (2-month) β-blocker withdrawal. Therefore, the 14 patients of the present study were comparable with 8 CHF patients on carvedilol provided by Agostoni and coworkers (Fig. 1, Group B, from reference 7).

Our patients were well matched to Agostoni’s cohort with respect to age (49 ± 8 vs. 50 ± 9, respectively, P = .8), peak VO₂ (15.9 ± 3.0 vs. 16.5 ± 3.8, respectively, P = .7), peak HR (72 ± 11 vs. 78 ± 15% predicted, respectively, P = .4), peak V’E (49.6 ± 9.9 vs. 45.5 ± 14.5, respectively, P = .5), and V’EE/VO₂ slope (31.6 ± 7.9 vs. 30.6 ± 3.9, respectively, P = .7) in the BBOFF condition, as well as in the BBON condition (peak VO₂ = 15.5 ± 2.9 vs. 17.7 ± 7.1, respectively, P = .4; peak HR = 68 ± 10 vs. 72 ± 16% predicted, respectively, P = .6; peak V’E = 45.8 ± 8.6 vs. 43.6 ± 19.2, respectively, P = .8), and V’EE/VO₂ slope = 29.4 ± 5.9 vs. 26.8 ± 3.8, respectively, P = .2). When analyzing both groups separately or in combination, the difference (Δ) in peak HR between BBOFF and BBON did not correlate with the Δ in V’EE/VO₂ slope between BBOFF and BBON, nor with the Δ in peak V’E between BBOFF and BBON (Fig. 4A, B). The Δ peak HR did not correlate with Δ peak VO₂, expressed either as mL/min or as mL-kg-min (r = 0.19, P = .4 and r = 0.28, P = .2, respectively). The Δ peak V’E and Δ V’EE/VO₂ slope correlated both with Δ peak PETCO₂ (r = −0.82, P = .000003 and r = −0.73, P = .0001, respectively). Of note, the Δ V’EE/VO₂ slope also correlated with Δ maximal PETCO₂ (r = −0.55, P = .01). The Δ V’EE/VO₂ slope did not correlate with Δ peak VO₂, expressed either as mL/min or as mL-kg-min (r = −0.07, P = .7 and r = −0.01, P = .9, respectively).

**Discussion**

The main findings of this study are as follows. 1) Acute β-blocker withholding worsened ventilatory efficiency in CHF patients during exercise; 2) acute β-blocker withholding did not modify the ventilation/perfusion mismatching during exercise; 3) acute β-blocker withholding was associated with an increase of reflex regulation of V’E (V’CO₂ independent); and 4) correlative analysis did not show an association between change in peak HR and change in peak V’E or in V’EE/VO₂ slope.

Based on Weber classification of severity, our patients with advanced CHF demonstrated mild-to-severe exercise intolerance which was not affected by acute β-blocker withholding (VO₂/kg peak, 15.6 ± 2.8 vs. 16.0 ± 2.7; Table 2). We were satisfied that the reduced exercise performance in our CHF patients was not the result of reduced motivational effort: under both conditions, patients reported intolerable exertional symptoms at the peak of exercise and showed an RER > 1.0 at peak exercise.

During exercise, V’E was higher at peak (by 3.5 L/min, P = .04) and at maximal PETCO₂ (by 2.2 L/min, P = .002), and V’EE/VO₂ slope was steeper (30.8 ± 7.4 vs. 29.1 ± 5.4, P = .04) in CHF patients after acute β-blocker withholding (Fig. 1). We considered the following potential contributors to reduced ventilatory efficiency after acute β-blocker withholding: 1) early local metabolic acidosis, reflecting reduced

Table 2. Metabolic and Cardiorespiratory Responses to CPET in CHF Patients (n = 17) with (BBON) and without β-blockers (BBOFF)

<table>
<thead>
<tr>
<th>Variables</th>
<th>BBOFF</th>
<th>BBON</th>
<th>BBOFF</th>
<th>BBON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, seconds</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>VO₂, mL/min</td>
<td>308 ± 101</td>
<td>280 ± 75</td>
<td>953 ± 188</td>
<td>967 ± 162</td>
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<tr>
<td>VO₂/kg</td>
<td>3.6 ± 0.8</td>
<td>3.4 ± 1.1</td>
<td>1391 ± 460</td>
<td>1342 ± 393</td>
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<tr>
<td>V’CO₂, mL/min</td>
<td>262 ± 85</td>
<td>255 ± 92</td>
<td>16.0 ± 2.7</td>
<td>15.6 ± 2.8</td>
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<tr>
<td>RER</td>
<td>0.85 ± 0.06</td>
<td>0.90 ± 0.1</td>
<td>1458 ± 459</td>
<td>1414 ± 429</td>
</tr>
<tr>
<td>HR, beats/min (% pred)</td>
<td>73 ± 13 (44 ± 9)</td>
<td>67 ± 13 (40 ± 8)*</td>
<td>11.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>O₂ pulse, mL/beat</td>
<td>4.4 ± 2.2</td>
<td>4.3 ± 1.6</td>
<td>123 ± 18 (73 ± 10)</td>
<td>114 ± 16* (68 ± 9)*</td>
</tr>
<tr>
<td>V’E, L/min</td>
<td>10.3 ± 2.8</td>
<td>10.2 ± 3.8</td>
<td>113.1 ± 3.1</td>
<td>11.9 ± 5.5</td>
</tr>
<tr>
<td>R’ (breaths/min)</td>
<td>19 ± 6</td>
<td>17 ± 6</td>
<td>49.5 ± 10.7</td>
<td>46.1 ± 9.6*</td>
</tr>
<tr>
<td>V’ₚ/VO₂ ratio</td>
<td>34 ± 6</td>
<td>36 ± 8</td>
<td>38 ± 9</td>
<td>37 ± 10</td>
</tr>
<tr>
<td>V’ₚ/V’CO₂ ratio</td>
<td>40 ± 7</td>
<td>41 ± 7</td>
<td>1.34 ± 0.32</td>
<td>1.32 ± 0.37</td>
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<tr>
<td>P₄O₂</td>
<td>108 ± 7</td>
<td>108 ± 8</td>
<td>38 ± 14</td>
<td>36 ± 11</td>
</tr>
<tr>
<td>P₄CO₂</td>
<td>34.4 ± 3.0</td>
<td>34.1 ± 3.5</td>
<td>36 ± 10</td>
<td>34 ± 8</td>
</tr>
<tr>
<td>P₄O₂</td>
<td>113 ± 9</td>
<td>112 ± 7</td>
<td>113 ± 9</td>
<td>112 ± 7</td>
</tr>
<tr>
<td>P₄CO₂</td>
<td>34.1 ± 6.4</td>
<td>35.2 ± 4.7</td>
<td>34.1 ± 6.4</td>
<td>35.2 ± 4.7</td>
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</table>

CPET, cardiopulmonary exercise tolerance testing; CHF, chronic heart failure; BBON, 3 hours after administration of β-blocker; BBOFF, 27 hours after the last β-blocker ingestion; VO₂, oxygen uptake; V’CO₂, carbon dioxide production; RER, respiratory exchange ratio; HR, heart rate; V’E, ventilation; R’; respiratory frequency; Vₚ, tidal volume; P₄O₂, end-tidal partial pressure for oxygen; P₄CO₂, end-tidal partial pressure for carbon dioxide.

*P < .05.
Table 3. Metabolic and Cardiorespiratory Responses to CPET in CHF Patients (n = 17) with (BBON) and without β-blockers (BBOFF).

<table>
<thead>
<tr>
<th>Variables</th>
<th>BBON</th>
<th>BBOFF</th>
</tr>
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<tbody>
<tr>
<td>V̇O₂/kg</td>
<td>12.8 ± 2.4</td>
<td>12.5 ± 2.7</td>
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<tr>
<td>VO₂/Ag</td>
<td>10.1 ± 2.0</td>
<td>10.5 ± 2.0</td>
</tr>
<tr>
<td>RER</td>
<td>0.9 ± 0.05</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>ṖETO₂</td>
<td>4.7 ± 3.7</td>
<td>5.8 ± 3.6</td>
</tr>
<tr>
<td>ṖETO₂</td>
<td>105 ± 4.7</td>
<td>105 ± 5.8</td>
</tr>
</tbody>
</table>

The V̇E/VCO₂ slopes (V̇E/V̇CO₂) are shown in all patients during BBON (27 hours after the last β-blocker ingestion) and BBOFF (3 hours after administration of β-blocker) conditions.

One possible explanation for our findings may lie in the pulmonary vasodilatory effect of β-blocker, especially carvedilol, because of its α-blocking properties (14 of 17 patients were on carvedilol). Upon withdrawal, pulmonary vasoconstriction may occur; therefore, pulmonary perfusion may decrease, leading to a ventilation/perfusion mismatching, which would in turn increase the V̇E/V̇CO₂ slope. However, it should be noted that acute β-blocker withholding was associated with consistent increase in V̇E/V̇CO₂ slope in the absence of any measurable deterioration in pulmonary gas exchange; both ṖETO₂ and ṖETO₂ were preserved at rest, at AT, at RC and at peak exercise (Tables 2, 3). The V̇E/V̇O₂ and V̇E/V̇CO₂ ratios were also not different throughout exercise under the 2 conditions (Tables 2, 3), thus suggesting that the increased ventilatory requirement observed after acute β-blocker withholding was less likely to reflect the increased ventilation/perfusion mismatching as a result of reduced ability to decrease a higher physiological dead space during exercise due to reduced pulmonary perfusion. Of note, V̇T expansion during exercise did not differ under both conditions, thus being unlikely that V̇T could also have contributed to the high physiological dead space (Tables 2, 3).

Fig. 1. Individual ventilation (V̇E) and carbon dioxide production (V̇CO₂) slopes (V̇E/V̇CO₂ slopes) are shown in all patients during BBOFF (27 hours after the last β-blocker ingestion) and BBON (3 hours after administration of β-blocker) conditions.
The steepness with which $V'_E$ rises with respect to $V'_0 CO_2$ is also determined by the behavior of arterial CO2 tension and the $V'_0 CO_2$ during exercise. Having reasonably excluded the previously mentioned mechanisms and given that acute $\beta$-blocker withholding did not modify the $V'_0 CO_2$ throughout exercise in our study, we can infer that the slope of the $V'_E/V'_0 CO_2$ relationship would have substantially increased if PaCO2 was driven down by a high ventilatory drive from overactive peripheral chemoreceptors or by overactive metabo- or ergoreceptors in exercising skeletal muscles. The CO2 set point can be noninvasively estimated by the PETCO2 during exercise before the metabolic compensation point is reached. This point, that we called maximal PETCO2, is the highest value of PETCO2 recorded during an incremental exercise test, and was observed between the AT and the RC point when the PETCO2 remains constant (Table 3). The observation that after acute $\beta$-blocker withholding the recorded maximal PETCO2 was 1.1 mm Hg lower ($P = .03$) and $V'_E$ was 2.2 L/min higher ($P = .002$) with an unchanged $V'_0 CO_2$ (Table 3) strongly favors a decrease in CO2 set point, likely from an increased excitatory inputs on $V'_E$ caused by the restoration of the overactive chemo- and metabo- and ergoreflexes, which are driven by the sympathetic nervous system activity.25–28

The contention that acute $\beta$-blocker withholding exerted its effect more on chemo-, metabo-, or ergo-receptors rather than on $\beta_1$-blockade, is also supported by the lack of correlation between delta peak HR (an excellent in vivo measure of $\beta$-blockade22) and either delta peak $V'_E$ or delta $V'_E/V'_0 CO_2$ slope (Fig. 2). Comparison of our data on acute (24-hour) $\beta$-blocker withholding with historical data kindly provided by Agostoni and colleagues (Fig. 1, Group B, from reference 7) on chronic (2-month) $\beta$-blocker withholding suggests the
same mechanisms and interpretations (Fig. 4), i.e., that the decreased ventilatory efficiency is likely from an increase of V\textsubscript{0}\textsubscript{CO\textsubscript{2}}-independent regulation of V\textsubscript{E}.

**Limitations**

The number of patients of the present study is limited; therefore, we must be very circumspect in any generalization of our findings to the larger CHF population. The lack of measurement of central hemodynamics and Pa\textsubscript{CO\textsubscript{2}} during exercise precludes a definitive assessment of the effect of acute (24-hour) \(\beta\)-blocker withholding on ventilation/perfusion mismatching and on regulation of CO\textsubscript{2} set point during exercise. Our use of unpublished data to evaluate a unified mechanism is somewhat unusual. However, we feel it is acceptable as the unpublished data derive from a previously published study\textsuperscript{7} and 1 of the authors participated in the current study and can vouch for the similarity of experimental conditions and data collection as the present study.\textsuperscript{7} We believe the use of these data is reasonable with the caveat that interpretation to the larger heart failure population should be made with caution. Further studies that contain a larger sample size and engage measurement of central hemodynamics and Pa\textsubscript{CO\textsubscript{2}} during exercise will be required to definitively elucidate the physiological mechanisms of the decreased ventilatory efficiency after \(\beta\)-blocker withholding.

**Conclusion**

The current study extends previous studies on the physiological mechanisms of \(\beta\)-blocker efficacy by exploring the interaction between the ventilatory efficiency and ventilation/perfusion mismatching and regulation of CO\textsubscript{2} set point during exercise. Our results suggest that both acute and chronic \(\beta\)-blocker withholding produce decreased ventilatory efficiency, mostly from an increase of V\textsubscript{0}\textsubscript{CO\textsubscript{2}}-independent regulation of V\textsubscript{E} and less likely from a change in ventilation/perfusion mismatching. Further studies are required to determine the clinical implications of the pharmacologically induced interactions that we have described.

**Disclosures**

None.

**References**


