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 (BB_{ON}) or 27 hours after the last β-blocker ingestion (BB_{OFF}). The ventilatory efficiency was measured via the slope of the linear relationship between ventilation (V'_E) and carbon dioxide production ($V'CO_2$) (ie, $V'_E/V'CO_2$ slope). Measurements were also made at rest, anaerobic threshold (AT), maximal end-tidal pressure for carbon dioxide ($P_{ET}CO_{2max}$), respiratory compensation point (RC), and peak exercise. Compared with BB_{ON}, the $V'_E/V'CO_2$ slope was significantly increased during BB_{OFF} (30.8 ± 7.4 vs. 29.1 ± 5.4, $P = .04$). At peak exercise, oxygen uptake ($V'O_2$, 16.0 ± 2.7 vs. 15.6 ± 2.8 mL·kg·min) and $V'CO_2$ (1458 ± 459 vs. 1414 ± 429 mL/min) were not different between the 2 conditions, whereas V'_E was higher during BB_{OFF} (49.5 ± 10.7 vs. 46.1 ± 9.6 L/min, $P = .04$). No differences were noted at AT and RC in $V'O_2$, $V'CO_2$, V'_E, $V'_E/V'O_2$, and $V'_E/V'CO_2$ ratios during the 2 conditions. At $P_{ET}CO_{2max}$, used to noninvasively estimate the CO_2 set point, V'_E was higher (33.9 ± 7.6 vs. 31.7 ± 7.3 L/min, $P = .002$) and $P_{ET}CO_2$ was lower (37.4 ± 4.8 vs. 38.5 ± 4.0 mm Hg, $P = .03$), whereas $V'CO_2$ was unchanged (1079 ± 340 vs. 1050 ± 322 mL/min) during BB_{OFF}.

Conclusion: Acute β-blocker withholding resulted in decreased ventilatory efficiency mostly from an increase of $V'CO_2$-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 (ie, the $V'_E/V'CO_2$ 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 $V'_E/V'CO_2$ slope is a strong prognostic marker independent from other exercise related heart failure prognostic markers such as peak oxygen uptake ($V'O_2$).[3,5]

Long-term treatment with β-blockers has been shown to reduce the $V'_E/V'CO_2$ 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 ($PaCO_2$) set point (which is in part controlled by sympathetic nervous system activity[7,8]) have been advocated as potential contributory factors.[6,7]

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 density[11–14] 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

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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 coworkers[7] 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 (BB_{ON}), whereas the other test was performed 27 hours after the last β-blocker ingestion (BB_{OFF}). BB_{ON} and BB_{OFF} 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). V'_E, $V'O_2$, $V'CO_2$, end-tidal oxygen and carbon dioxide partial pressure ($P_{ET}O_2$ and $P_{ET}CO_2$, respectively), tidal volume (V_T), 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 $V'O_2$ ($V'O_{2peak}$) and peak V'_E (V'_{Epeak}) were defined, respectively, as the highest value of $V'O_2$ and V'_E 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 $V'O_2$ at which the ventilatory equivalent for oxygen ($V'_E/V'O_2$) begins to increase systematically without an increase in the ventilatory equivalent for carbon dioxide ($V'_E/V'CO_2$) and where $P_{ET}O_2$ begins to increase without a decrease in $P_{ET}CO_2$.[18] The respiratory compensation point (*RC*) was calculated as the point where the slope of the $V'_E/V'CO_2$ relationship started to increase.[18] The maximal $P_{ET}CO_2$ was defined as the highest value of $P_{ET}CO_2$ observed during exercise test, between the *AT* and the *RC* point, when $P_{ET}CO_2$ remains constant.[18] This was done to evaluate the CO_2 set point, which can be noninvasively estimated by the $P_{ET}CO_2$ during exercise before the metabolic compensation point is reached. Exercise capacity was assessed by measuring the $V'O_2$ at *AT* and peak. Mismatching of the heart and lungs was evaluated via the ventilatory efficiency measure $V'_E/V'CO_2$ slope (ie, the slope of the linear relationship between V'_E and $V'CO_2$ 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 $P_{ET}CO_2$; 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 $P_{ET}CO_2$, 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 V'_E, $V'_E/V'CO_2$ 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

Subjects' characteristics are summarized in Table 1.

Cardiovascular Response to CPET

Differences in cardiovascular responses at rest and at peak exercise after BB_{OFF} compared with BB_{ON} are shown in Table 2. Based on Weber classification of severity,[19,20] 1 patient presented with $V'O_2$ at *AT* >14 mL·min·kg and $V'O_2$ peak >20 mL·min·kg (Class A, little or no impairment), 9 patients with $V'O_2$ at *AT* falling between 11 and 14 mL·min·kg and $V'O_2$ peak between 16 and 20 mL·min·kg (Class B, mild-to-moderate impairment), whereas 7 patients presented with $V'O_2$ at *AT* falling between 8 and 11 mL·min·kg and $V'O_2$ peak between 10 and 16 mL·min·kg (Class C, moderate-to-severe impairment) during BB_{OFF}. BB_{ON} did not affect exercise capacity; $V'O_2$ peak, $V'O_2$ at *AT* and time to exhaustion were unaffected by BB_{ON} (Tables 2, 3). BB_{OFF} patients presented at rest with higher HR, by 6 ± 6 beats/min (~8%, P = .0006), compared with BB_{ON} patients, but with no difference in resting $V'O_2$ (Table 2). BB_{OFF} 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 $P_{ET}CO_2$, and *RC* point after β-blockers withholding compared with BB_{ON} are shown in Table 3. Rest-to-peak changes in HR ranged from 50 ± 21 beats/min during BB_{OFF} session to 47 ± 17 beats/min during BB_{ON} 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 $V'CO_2$, V_T, and R*f* after β-blocker withholding compared with BB_{ON} (Table 2). Rest-to-peak changes in V'_E ranged from 39.2 ± 9.5 L/min during BB_{OFF} session to 35.9 ± 9.3 L/min during BB_{ON} session. At maximal $P_{ET}CO_2$, which was observed between the *AT* and the *RC* point, V'_E was 2.2 L/min higher (P = .002) and $P_{ET}CO_2$ 1.1 mm Hg lower (P = .03), whereas $V'CO_2$ was not significantly changed after β-blocker withholding (Table 3).

β-blocker withholding did also increase the $V'_E/V'CO_2$ 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 $V'_E/V'CO_2$ slope ≤29.9 (VC I), 6 patients with $V'_E/V'CO_2$ slope between 30.0 and 35.9 (VC II), 1 patient with $V'_E/V'CO_2$ slope between 36.0 and 44.9 (VC III), and 1 patient with $V'_E/V'CO_2$ slope ≥ 45.0 (VC IV) during BB_{OFF}. During BB_{ON}, 11 patients showed a $V'_E/V'CO_2$ slope ≤ 29.9 (VC I), 4 patients a $V'_E/V'CO_2$ slope between 30.0 and 35.9 (VC II), and 2 patients a $V'_E/V'CO_2$ slope between 36.0 and 44.9 (VC III), whereas no one showed a $V'_E/V'CO_2$ slope ≥ 45.0 (VC IV).

The ventilatory equivalents for oxygen and carbon dioxide ($V'_E/V'O_2$ and $V'_E/V'CO_2$, respectively) were not significantly different during BB_{OFF} session compared with BB_{ON} session at rest and at peak exercise (Table 2), as well as at *AT* ($V'_E/V'O_2$ = 30 ± 7 vs. 29 ± 5; $V'_E/V'CO_2$ = 32 ± 7 vs. 32 ± 5), and at *RC* point ($V'_E/V'O_2$ = 34 ± 11 vs. 32 ± 7; $V'_E/V'CO_2$ = 33 ± 8 vs. 32 ± 6) (Table 3). No differences were also found in $P_{ET}O_2$ and $P_{ET}CO_2$ values at the previously mentioned levels of exercise in both sessions. Both $V'_E/V'O_2$ and $V'_E/V'CO_2$ ratios were ~2 units higher during BB_{OFF} sessions at maximal $P_{ET}CO_2$ because of the higher V'_E at this level of exercise (Table 3).

Correlates of Improvement

The difference (Δ) in peak HR between BB_{OFF} and BB_{ON}, an indicator of sinoatrial β_1-receptor blockade,[22] did not correlate with the Δ in $V'_E/V'CO_2$ slope between BB_{OFF} and BB_{ON} (r = -0.27, P = .3) (Fig. 2A), nor with the Δ in *peak* V'_E between BB_{OFF} and BB_{ON} (r = −0.23, P = .4) (Fig. 2B). The Δ peak HR did not correlate with Δ peak $V'O_2$, expressed either as mL/min (r = 0.25, P = .3) or as mL·kg·min (r = 0.31, P = .2). The Δ peak V'_E and Δ $V'_E/V'CO_2$ slope correlated both with Δ peak $P_{ET}CO_2$ (r = −0.826, P = .00004 and r = −0.791, P = .0002, respectively). Of note, the Δ $V'_E/V'CO_2$ slope also correlated with Δ maximal $P_{ET}CO_2$ (r = −0.64, P = .007), and Δ V'_E measured at maximal $P_{ET}CO_2$ correlated with Δ maximal $P_{ET}CO_2$ (r = −0.56, P = .03) (Fig. 3A, B). The Δ $V'_E/V'CO_2$ slope did not correlate with Δ peak $V'O_2$, expressed either as mL/min (r = −0.38, P = .1) or as mL·kg·min (r = −0.46, 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)

Table 1. Subjects' Characteristics (n = 17)

Male:Female	11:6
Age, y	51 ± 11
Height, cm	170 ± 11
Weight, kg	86 ± 21
Body mass index, kg/m^2	30 ± 6
LVEF	23 ± 8
ICM	8
NICM	9
Carvedilol	14
Bisoprolol	1
Metoprolol	2
Diuretics	9
Digoxin	3
ACE inhibitor	11
ARB	4
AA	8

LVEF, left ventricular ejection fraction; ICM, ischemic cardiomyopathy; NICM, nonischemic (idiopathic) cardiomyopathy; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptors blockers; AA, antialdosterone agents.

Values are means ± SD.

Table 2. Metabolic and Cardiorespiratory Responses to CPET in CHF Patients (n = 17) with (BB_{ON}) and without β-blockers (BB_{OFF})

Variables	Rest		Peak	
	BB_{OFF}	BB_{ON}	BB_{OFF}	BB_{ON}
Time, seconds	—	—	953 ± 188	967 ± 162
$V'O_2$, mL/min	308 ± 101	280 ± 75	1391 ± 460	1342 ± 393
$V'O_2$/kg	3.6 ± 0.8	3.4 ± 1.1	16.0 ± 2.7	15.6 ± 2.8
$V'CO_2$, mL/min	262 ± 85	255 ± 92	1458 ± 459	1414 ± 429
RER	0.85 ± 0.06	0.90 ± 0.1	1.1 ± 0.1	1.1 ± 0.1
HR, beats/min (% pred)	73 ± 13 (44 ± 9)	67 ± 13* (40 ± 8)*	123 ± 18 (73 ± 10)	114 ± 16* (68 ± 9)*
O_2 pulse, mL/beat	4.4 ± 2.2	4.3 ± 1.6	11.3 ± 3.1	11.9 ± 3.5
V'_E, L/min	10.3 ± 2.8	10.2 ± 3.8	49.5 ± 10.7	46.1 ± 9.6*
R*f* (breaths/min)	19 ± 6	17 ± 6	38 ± 9	37 ± 10
V_T, L	0.59 ± 0.23	0.64 ± 0.29	1.34 ± 0.32	1.32 ± 0.37
$V'_E/V'O_2$ ratio	34 ± 6	36 ± 8	38 ± 14	36 ± 11
$V'_E/V'CO_2$ ratio	40 ± 7	41 ± 7	36 ± 10	34 ± 8
$P_{ET}O_2$	108 ± 7	108 ± 8	113 ± 9	112 ± 7
$P_{ET}CO_2$	34.4 ± 3.0	34.1 ± 3.5	34.1 ± 6.4	35.2 ± 4.7

CPET, cardiopulmonary exercise tolerance testing; CHF, chronic heart failure; BB_{ON}, 3 hours after administration of β-blocker; BB_{OFF}, 27 hours after the last β-blocker ingestion; $V'O_2$, oxygen uptake; $V'CO_2$, carbon dioxide production; RER, respiratory exchange ratio; HR, heart rate; V'_E, ventilation; R*f*, respiratory frequency; V_T, tidal volume; $P_{ET}O_2$, end-tidal partial pressure for oxygen; $P_{ET}CO_2$, end-tidal partial pressure for carbon dioxide.

Values are means ± SD.

*$P < .05$.

β-blocker withholding[7] 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 $V'O_2$ (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 $V'_E/V'CO_2$ slope (31.6 ± 7.9 vs. 30.6 ± 3.9, respectively, $P = .7$) in the BB_{OFF} condition, as well as in the BB_{ON} condition (peak $V'O_2$ = 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 $V'_E/V'CO_2$ 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 BB_{OFF} and BB_{ON} did not correlate with the Δ in $V'_E/V'CO_2$ slope between BB_{OFF} and BB_{ON}, nor with the Δ in *p*eak V'_E between BB_{OFF} and BB_{ON} (Fig. 4A, B). The Δ peak HR did not correlate with Δ peak $V'O_2$, 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 $V'_E/V'CO_2$ slope correlated both with Δ peak $P_{ET}CO_2$ ($r = -0.82$, $P = .000003$ and $r = -0.73$, $P = .0001$, respectively). Of note, the Δ $V'_E/V'CO_2$ slope also correlated with Δ maximal $P_{ET}CO_2$ ($r = -0.55$, $P = .01$). The Δ $V'_E/V'CO_2$ slope did not correlate with Δ peak $V'O_2$, 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 ($V'CO_2$-independent); and 4) correlative analysis did not show an association between change in *peak* HR and change in peak V'_E or in $V'_E/V'CO_2$ slope.

Based on Weber classification of severity,[19,20] our patients with advanced CHF demonstrated mild-to-severe exercise intolerance which was not affected by acute β-blocker withholding ($V'O_2$/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 $P_{ET}CO_2$ (by 2.2 L/min, $P = .002$), and $V'_E/V'CO_2$ 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 3. Metabolic and Cardiorespiratory Responses to CPET in CHF Patients (n = 17) with (BB_{ON}) and without β-blockers (BB_{OFF})

Variables	Anaerobic Threshold		Maximal $P_{ET}CO_2$		Respiratory Compensation Point	
	BB_{OFF}	BB_{ON}	BB_{OFF}	BB_{ON}	BB_{OFF}	BB_{ON}
$V'O_2$, mL/min	1115 ± 358	1098 ± 323	1155 ± 359	1137 ± 324	1323 ± 454	1282 ± 388
$V'O_2$/kg	12.8 ± 1.9	12.7 ± 2.1	13.3 ± 2.0	13.2 ± 2.1	15.2 ± 2.7	14.8 ± 2.5
$V'CO_2$, mL/min	1016 ± 322	991 ± 276	1079 ± 340	1050 ± 322	1307 ± 443	1286 ± 396
RER	0.9 ± 0.05	0.9 ± 0.04	0.9 ± 0.04	0.9 ± 0.05	1.0 ± 0.1	1.0 ± 0.1
HR, beats/min (% pred)	111 ± 13 (65 ± 7)	102 ± 16* (60 ± 10)*	113 ± 14 (67 ± 8)	110 ± 15 (65 ± 9)	120 ± 17 (71 ± 9)	115 ± 14 (68 ± 8)
O_2 pulse, mL/beat	10.0 ± 2.8	10.8 ± 2.9*	10.2 ± 2.9	10.4 ± 2.8	11.0 ± 3.2	11.2 ± 3.4
V'_E, L/min	31.8 ± 7.1	30.7 ± 6.7	33.9 ± 7.6	31.7 ± 7.3*	41.9 ± 10.3	40.2 ± 9.4
Rf (breaths/min)	29 ± 7	28 ± 6	31 ± 8	30 ± 8	35 ± 8	33 ± 8
V_T, L	1.13 ± 0.37	1.14 ± 0.32	1.14 ± 0.35	1.13 ± 0.38	1.23 ± 0.29	1.25 ± 0.36
$V'_E/V'O_2$ ratio	30 ± 7	29 ± 5	30 ± 6	28 ± 4*	34 ± 11	32 ± 7
$V'_E/V'CO_2$ ratio	32 ± 7	32 ± 5	33 ± 6	31 ± 5*	33 ± 8	32 ± 6
$P_{ET}O_2$	105 ± 7	105 ± 8	105 ± 6	104 ± 7	109 ± 8	109 ± 7
$P_{ET}CO_2$	37.2 ± 4.7	37.6 ± 4.2	37.4 ± 4.8	38.5 ± 4.0*	35.9 ± 5.8	36.6 ± 4.6

See Table 2 for abbreviations.
Values are means ± SD.
*$P < .05$.

oxygen delivery/utilization; 2) increased ventilation/perfusion mismatching, reflecting reduced cardiac output or increased central venous distension/congestion; 3) decrease in CO_2 set point, caused by the reversion to the overactive chemo- and metabo- and ergo- reflexes, which are driven by the sympathetic nervous system activity; or 4) a combination of these.

In the current study, acute β-blocker withholding did not delay the occurrence of the anaerobic threshold and $V'O_2$ and V'_E measured at this point (Table 3) were not different between the 2 conditions, suggesting that the reduced ventilatory efficiency was unlikely to be related to an early local metabolic acidosis that, in turn, would have reflected a reduced oxygen delivery/utilization to the peripheral exercising muscles.

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).[23] Upon withdrawal, pulmonary vasoconstriction may occur; therefore, pulmonary perfusion may decrease, leading to a ventilation/perfusion mismatching, which would in turn increase the $V'_E/V'CO_2$ slope.[6,7,17,24] However, it should be noted that acute β-blocker withholding was associated with consistent increase in $V'_E/V'CO_2$ slope in the absence of any measurable deterioration in pulmonary gas exchange; both $P_{ET}O_2$ and $P_{ET}CO_2$ were preserved at rest, at *AT*, at *RC* and at peak exercise (Tables 2, 3). The $V'_E/V'O_2$ and $V'_E/V'CO_2$ 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, V_T expansion during exercise did not differ under both conditions, thus being unlikely that V_T could also have contributed to the high physiological dead space (Tables 2, 3).[17]

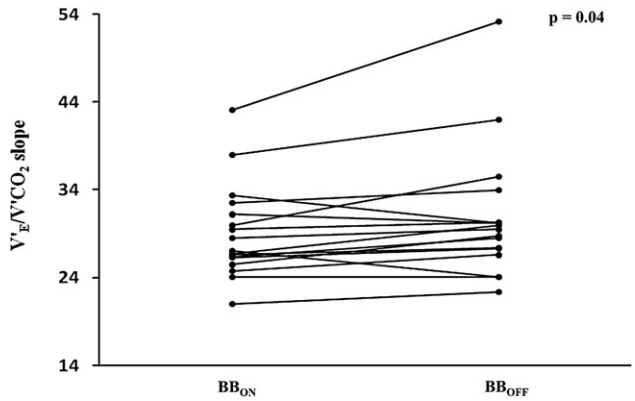

Fig. 1. Individual ventilation (V'_E) and carbon dioxide production ($V'CO_2$) slopes ($V'_E/V'CO_2$ slopes) are shown in all patients during BB_{OFF} (27 hours after the last β-blocker ingestion) and BB_{ON} (3 hours after administration of β-blocker) conditions.

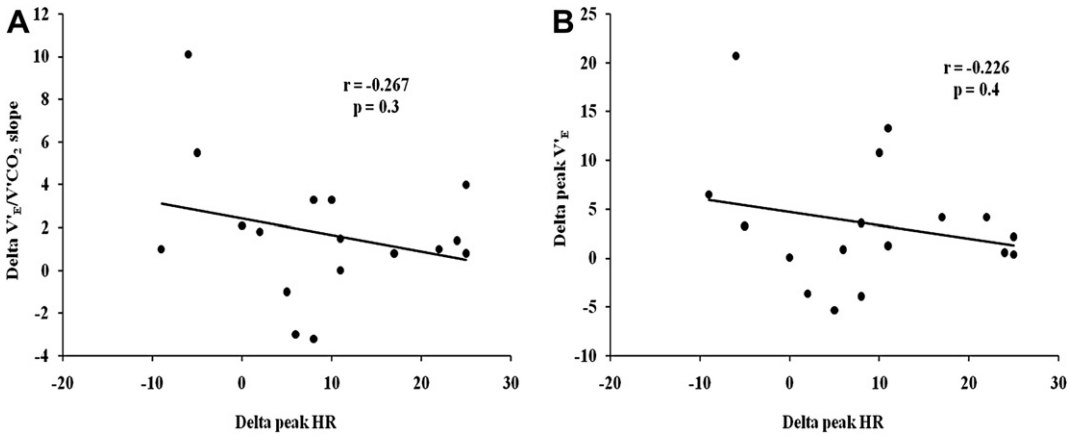

Fig. 2. (A) Correlation between the difference (delta) in peak heart rate (HR) between BB_{OFF} (27 hours after the last β-blocker ingestion) and BB_{ON} (3 hours after administration of β-blocker) and delta in ventilation (V'_E) and carbon dioxide production ($V'CO_2$) slope ($V'_E/V'CO_2$ slope) between BB_{OFF} and BB_{ON} ($r = -0.267$, $P = .3$) in our 17 chronic heart failure (CHF) patients (filled circles). (B) Correlation between delta in peak HR between BB_{OFF} and BB_{ON} and delta in peak V'_E between BB_{OFF} and BB_{ON} ($r = -0.226$, $P = .4$) in our 17 CHF patients (filled circles).

The steepness with which V'_E rises with respect to $V'CO_2$ is also determined by the behavior of arterial CO_2 tension and the $V'CO_2$ during exercise. Having reasonably excluded the previously mentioned mechanisms and given that acute β-blocker withholding did not modify the $V'CO_2$ throughout exercise in our study, we can infer that the slope of the $V'_E/V'CO_2$ relationship would have substantially increased if $PaCO_2$ was driven down by a high ventilatory drive from overactive peripheral chemoreceptors or by overactive metabo- or ergoreceptors in exercising skeletal muscles. The CO_2 set point can be noninvasively estimated by the $P_{ET}CO_2$ during exercise before the metabolic compensation point is reached. This point, that we called maximal $P_{ET}CO_2$, is the highest value of $P_{ET}CO_2$ recorded during an incremental exercise test, and was observed between the *AT* and the *RC* point when the $P_{ET}CO_2$ remains constant (Table 3). The observation that after acute β-blocker withholding the recorded maximal $P_{ET}CO_2$ was 1.1 mm Hg lower ($P = .03$) and V'_E was 2.2 L/min higher ($P = .002$) with an unchanged $V'CO_2$ (Table 3) strongly favors a decrease in CO_2 set point, likely from an increased excitatory inputs on V'_E caused by the restoration of the overactive chemo- and metabo- and ergo-reflexes, which are driven by the sympathetic nervous system activity.[25–28]

The contention that acute β-blocker withholding exerted its effect more on chemo-, metabo-, or ergo-receptors rather than on β_1-blockade, is also supported by the lack of correlation between delta peak HR (an excellent in vivo measure of β-blockade[22]) and either delta peak V'_E or delta $V'_E/V'CO_2$ slope (Fig. 2). Comparison of our data on acute (24-hour) β-blocker withholding with historical data kindly provided by Agostoni and colleagues (Fig. 1, Group B, from reference 7) on chronic (2-month) β-blocker withholding suggests the

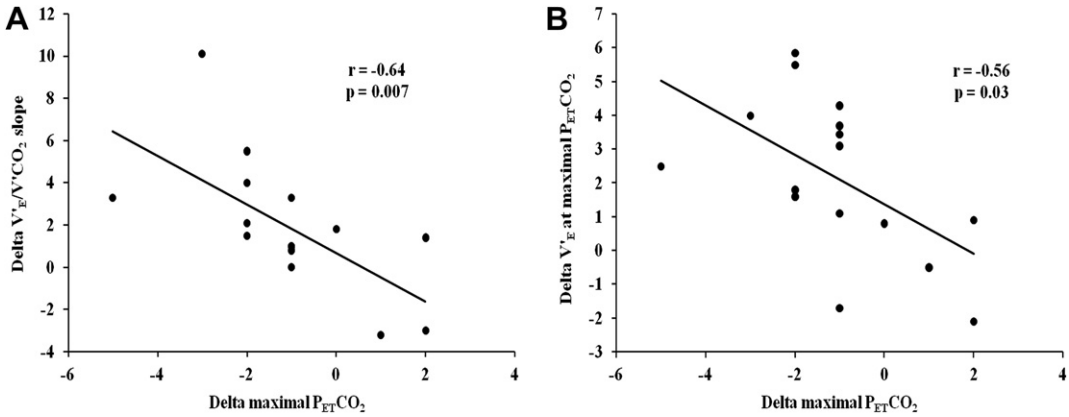

Fig. 3. (A) Correlation between the difference (delta) in end-tidal partial pressure for carbon dioxide ($P_{ET}CO_2$) between BB_{OFF} (27 hours after the last β-blocker ingestion) and BB_{ON} (3 hours after administration of β-blocker) measured at maximal $P_{ET}CO_2$ and delta in ventilation (V'_E) and carbon dioxide production ($V'CO_2$) slope ($V'_E/V'CO_2$ slope) between BB_{OFF} and BB_{ON} ($r = -0.64$, $P = .007$) in our 17 chronic heart failure (CHF) patients (filled circles). (B) Correlation between delta in $P_{ET}CO_2$ between BB_{OFF} and BB_{ON} and delta in V'_E between BB_{OFF} and BB_{ON} both measured at maximal $P_{ET}CO_2$ ($r = -0.56$, $P = .03$) in our 17 CHF patients (filled circles).

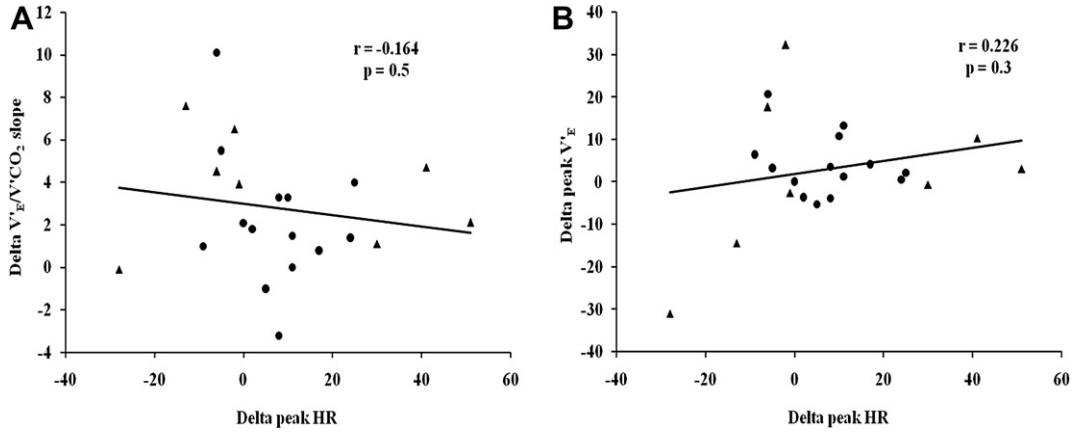

Fig. 4. (A) Correlation between delta in peak heart rate (HR) between BB_{OFF} (27 hours after the last β-blocker ingestion) and BB_{ON} (3 hours after administration of β-blocker) and delta in ventilation (V'_E) and carbon dioxide production ($V'CO_2$) slope ($V'_E/V'CO_2$ slope) between BB_{OFF} and BB_{ON} ($r = -0.164$, $P = .5$) in our 14 chronic heart failure (CHF) patients on carvedilol (filled circles) pooled with the 8 CHF patients on carvedilol from Agostoni[7] (filled triangles). (B) Correlation between delta in peak HR between BB_{OFF} and BB_{ON} and delta in peak V'_E between BB_{OFF} and BB_{ON} ($r = 0.226$, $P = .3$) in our 14 CHF patients on carvedilol (filled circles) pooled with the 8 CHF patients on carvedilol from Agostoni[7] (filled triangles).

same mechanisms and interpretations (Fig. 4), ie, that the decreased ventilatory efficiency is likely from an increase of $V'CO_2$-independent regulation of V'_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 $PaCO_2$ during exercise precludes a definitive assessment of the effect of acute (24-hour) β-blocker withholding on ventilation/perfusion mismatching and on regulation of CO_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[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.[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 $PaCO_2$ during exercise will be required to definitively elucidate the physiological mechanisms of the decreased ventilatory efficiency after β-blocker withholding.

Conclusion

The current study extends previous studies on the physiological mechanisms of β-blocker efficacy by exploring the interaction between the ventilatory efficiency and ventilation/perfusion mismatching and regulation of CO_2 set point during exercise. Our results suggest that both acute and chronic β-blocker withholding produce decreased ventilatory efficiency, mostly from an increase of $V'CO_2$-independent regulation of V'_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.

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