Effect of \(\beta\)-Blocker Cessation on Chronotropic Incompetence and Exercise Tolerance in Patients With Advanced Heart Failure

Benjamin J. Hirsh, MD; Andrea Mignatti, MD; A. Reshad Garan, MD; Nir Uriel, MD; Paolo Colombo, MD; Daniel B. Sims, MD; Ulrich P. Jorde, MD

Background—Chronotropic incompetence is defined as the inability to reach 80% of heart rate (HR) reserve or 80% of the maximally predicted HR during exercise. The presence of chronotropic incompetence is associated with reduced peak oxygen consumption, and rate–responsive pacing therapy is under investigation to improve exercise capacity in heart failure (HF). However, uncertainty exists about whether chronotropic incompetence and reduced exercise tolerance in HF are attributable to \(\beta\)-blockade.

Methods and Results—Subjects with HF and receiving long-term \(\beta\)-blocker therapy underwent cardiopulmonary exercise tolerance testing under 2 conditions in random sequence: (1) after a 27-hour washout period (Off-BB) and (2) 3 hours after \(\beta\)-blocker ingestion (On-BB). Norepinephrine levels were drawn at rest and at peak exercise. \(\beta\)-response to norepinephrine was assessed using the chronotropic responsiveness index: \(\Delta\text{HR}/\Delta\log\text{norepinephrine}\). Nineteen patients with systolic HF (left ventricular ejection fraction, 22.8±7.7%) were enrolled. Mean age was 49.4±12.3 years. Average carvedilol equivalent dose was 29.1±17.0 mg daily. Peak HR off/on \(\beta\)-blockers was 62.7±18.7% and 51.4±18.2% HR reserve (\(P<0.01\)) and 79.1±11.0% and 70.3±12.3% maximally predicted HR (\(P<0.01\)). For the Off-BB and On-BB conditions, the respiratory exchange ratios were 1.05±0.06 and 1.05±0.10 (\(P=0.77\)), respectively, confirming maximal and near identical effort in both conditions. The peak oxygen consumption was 16.6±3.34 and 15.9±3.31 mL/kg/min (\(P=0.03\)), and the chronotropic responsiveness index was 19.3±7.2 and 16.2±7.1 (\(P=0.18\)).

Conclusions—Acute \(\beta\)-blocker cessation does not normalize the chronotropic response to exercise in patients with advanced HF and chronotropic incompetence. (Circ Heart Fail. 2012;5:560-565.)

Key Words: heart failure ♦ chronotropic incompetence ♦ \(\beta\)-blocker ♦ heart rate ♦ exercise

Chronotropic incompetence (CI), defined as an inadequate heart rate (HR) response to increased activity or demand, is prevalent in patients with advanced heart failure (HF). The putative mechanism underlying CI in HF is \(\beta\)-receptor down-regulation and desensitization in the presence of increased circulating catecholamines. Specifically, it has been shown that the ratio of change in HR to change in circulating norepinephrine (NE) level (\(\Delta\text{HR}/\Delta\log\text{NE}\)), a measure of \(\beta\)-receptor sensitivity, decreases progressively with the severity of HF.

Clinical Perspective on p 565

Nearly half of patients with HF manifest CI, and this percentage increases with the severity of HF. Some studies have suggested that abnormal HR response underlies exercise intolerance in HF. This finding has informed the development of new therapies, such as rate-responsive pacing, with the goal of improving exercise tolerance in this patient population.

However, in patients with HF who are taking \(\beta\)-blockers, controversy exists about whether CI and exercise intolerance are effects of disease progression alone or whether they also can be attributed to pharmacological \(\beta\)-blockade. Nonetheless, discontinuation of \(\beta\)-blockers to allow for a higher HR is problematic given the substantial survival benefit derived from these agents in HF.

An interesting conundrum results: Should we investigate rate-responsive pacing while administering \(\beta\)-blockers? To further clarify the physiological consequences of \(\beta\)-blocker therapy in patients with advanced HF, we examined the effects of acute \(\beta\)-blocker cessation on the prevalence of CI, the HR response to endogenously released NE, and exercise capacity in this patient population.

Methods

Study Population

All patients with systolic HF, New York Heart Association class II to IV, receiving \(\beta\)-blocker therapy (bisoprolol, carvedilol, or metoprolol) for ≥3 months referred for cardiopulmonary exercise tolerance testing (CPETT) were screened. All patients were followed at the Columbia...
β-blockers were routinely uptitrated by physicians or nurse practitioners unless limited by blood pressure, bradycardia, fatigue, or other symptoms, possibly attributable to β-blockers. Patients were excluded if they had any of the following: atrial fibrillation or atrial flutter, inability to exercise, hospital admission for HF or acute coronary syndrome in the past 90 days or symptoms of myocardial ischemia, or inability to undergo a treadmill exercise test (eg, severe obstructive pulmonary disease or severe osteoarthritis). CI was not a factor in enrollment. Carvedilol equivalent dose was calculated for patients treated with bisoprolol and metoprolol based on the equivalence ratios established by the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) study. The study protocol was approved by the Columbia University Medical Center institutional review board, and each subject provided informed written consent.

Study Protocol

Each subject underwent CPETT twice. One test was conducted 3 hours after administration of β-blocker. This time period was chosen for testing because carvedilol, metoprolol, and bisoprolol reach a peak concentration between 2 and 4 hours. The other test was administered 27 hours after the last β-blocker ingestion. Testing was separated by a 1-week interval, and the order of testing assignment was randomized for each patient to eliminate possible training effects. Eleven patients were randomized to the On-BB condition (3 hr after β-blocker) first and 12 patients were randomized to the Off-BB condition (after a 27-hr washout period) first.

Exercise Testing

Resting HR was obtained after 30 minutes of rest in a quiet, temperature-controlled room. Peak oxygen consumption (pVO2 [mL/kg per minute]) was then assessed during graded treadmill exercise. Expired gases were collected throughout exercise through a low-resistance mouthpiece, and VO2 was recorded on a breath-by-breath basis using a Medgraphics metabolic cart (Med graphics, Medical Graphics Corporation, St. Paul, MN). The instruments were calibrated before each test and were corrected for humidity, room temperature, and barometric pressure according to the manufacturer’s protocol. The work rate increased continuously as a ramp function by augmenting the speed and grade of the treadmill according to a modified Naughton protocol. Subjects were exercised to a symptom-limited maximum. HR and ECG were recorded continuously during exercise, and blood pressure was measured at rest, every 2 minutes during exercise, upon completion of exercise, and at 1 minute after completion of exercise. pVO2 was defined as the highest value of oxygen uptake attained in the final 20 seconds of exercise when the respiratory exchange ratio was ≥1.0. CI was defined using the percentage HR reserve formula and percentage maximally predicted HR formula, with a cutoff of ≤80% for both measures. The anaerobic threshold was identified by the V-slope method. Oxygen pulse was calculated by dividing pVO2 by HR at the time pVO2 was achieved, expressed as mL/heart beat. The chronotropic responsiveness index was calculated using the following formula: (peak HR−baseline HR)/log (peak NE−baseline NE). Measurement of NE

After an overnight fast, an 18- or 20-gauge angiocatheter was inserted into a forearm vein without the use of a tourniquet. A total of 30 cm3 of venous blood was collected in EDTA vials: 15 cm3 after 30 minutes of rest and an additional 15 cm3 during peak exercise. Samples were stored on ice until centrifugation and then frozen immediately at −80°C. NE was measured using high performance liquid chromatography.

Statistical Analysis

All analyses were performed using SPSS software. Continuous variables are expressed as mean±SD. Paired t tests and the Wilcoxon rank sum test were used for within-group comparisons of the outcome variables. ANOVA for repeated measures was used to assess differences in HR at different time points. Pearson coefficient was used for correlations. All tests were 2-sided, with a P value <0.05 used to define statistical significance. There were no multiple testing adjustments.

Results

Twenty-three subjects with advanced HF were enrolled. All subjects were receiving stable, maximally tolerated β-blocker therapy for >3 months. Only 2 of the subjects had a change in β-blocker dose within the 3 months before CPETT. In 1 of the subjects, carvedilol was changed from 3.125 mg BID to 6.25 mg BID 2 months before CPETT. In the other subject,
carvedilol was changed from 6.25 mg BID to 12.5 mg BID 6 weeks before CPETT.

The study protocol is outlined in Figure 1. Results of 2 subjects were excluded from final analysis because they were observed to be paced during testing: 1 subject while at rest and the other subject during CPETT. One subject’s results were excluded because of a cuff-leak in the mouthpiece observed during exercise. Another subject’s results were excluded because the subject did not return for the second testing condition. Baseline characteristics of the patients included in final analysis (n=19) are shown in Table 1.23

Comparison of outcomes between testing conditions is shown in Table 2. Paired t tests and nonparametric testing yielded similar results. In each condition, patients had near identical respiratory exchange ratio and exercise time. In the On-BB condition, patients had a lower resting HR, a smaller change in HR, a lower HR at anaerobic threshold, and a lower peak HR (Table 2). Elevated HRs were observed in the Off-BB condition at various work rates (Figure 2). Despite the elevated HRs observed in the Off-BB condition, no significant differences were observed in VO2 at anaerobic threshold and only a small difference in mean pVO2 was observed between conditions (Table 2). Furthermore, although pVO2 was slightly higher in the Off-BB condition, oxygen pulse, a measure of efficiency, was lower.

Table 1. Demographic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD or Sample Size (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.4±12.4</td>
</tr>
<tr>
<td>Men</td>
<td>12 (63.2)</td>
</tr>
<tr>
<td>Height, in</td>
<td>66.6±4.3</td>
</tr>
<tr>
<td>Weight, lb</td>
<td>192.5±48.3</td>
</tr>
<tr>
<td>LVEF</td>
<td>22.8±7.7</td>
</tr>
<tr>
<td>Median pVO2, mL/kg per minute</td>
<td>15.2</td>
</tr>
<tr>
<td>Cause of HF: ischemic</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>6 (31.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (11.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>9 (47.4)</td>
</tr>
<tr>
<td>PAD</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>COPD</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Baseline CrF (MDRD GFR &lt;60)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>15 (78.9)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Metoprolol XL</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Carvedilol equivalent dose</td>
<td>29.1±17.0</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>14 (73.7)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>6 (31.6)</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Statin</td>
<td>12 (63.2)</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; pVO2, peak oxygen consumption; HF, heart failure; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; PAD, peripheral arterial disease; COPD, chronic obstructive pulmonary disease; CrF, chronic renal failure; MDRD GFR, estimated glomerular filtration rate using modification of diet in renal disease formula22; ACE, angiotensin-converting enzyme.

Off-BB condition, no significant differences were observed in VO2 at anaerobic threshold and only a small difference in mean pVO2 was observed between conditions (Table 2). Furthermore, although pVO2 was slightly higher in the Off-BB condition, oxygen pulse, a measure of efficiency, was lower.

Although percentage maximally predicted HR and percentage HR reserve was higher after holding β-blockers, >75% of the patients with each condition had a value below the <80% cutoff value for establishing CI (Figure 3). The HR and blood pressure
response to orthostasis differed between conditions (Figure 4). HR recovery 1 minute after completion of exercise was similar in each condition (Table 2). Although there was a higher level of NE at peak exercise in the On-BB condition, there were no significant differences in baseline NE or the chronotropic responsiveness index between conditions (Table 2). Changes in HR correlated with \( p \text{VO}_2 \) in the On-BB (\( R=0.60; P=0.01 \)) and Off-BB condition (\( R=0.49; P=0.03 \)) (Figure 5A and 5B).

**Discussion**

We examined whether acute cessation of \( \beta \)-blockade in patients with advanced HF affects CI, exercise capacity, and the HR response to endogenous NE during exercise. To our knowledge, this is the first study to address the effect of acute \( \beta \)-blocker cessation on CI in patients with advanced HF treated long term with \( \beta \)-blockers, and our principal findings are as follows. First, although withdrawal of \( \beta \)-blockers increases peak HR during exercise, it does not normalize the chronotropic response, and CI persists. Second, efficiency decreases after withdrawal of \( \beta \)-blockade, as evidenced by a decreased oxygen pulse. Third, although \( \beta \)-blockers do affect orthostatic response, they do not affect HR recovery after exercise, indicating that they do not interfere with vagal reactivation or sympathetic withdrawal. Last, the impaired HR response to increasing NE levels (ie, the chronotropic responsiveness index) during exercise is not affected by acute \( \beta \)-blocker withdrawal in patients with HF on long-term \( \beta \)-blocker therapy.

Several earlier studies, albeit mostly of a cross-sectional, retrospective nature and of relatively healthier patient populations, have failed to demonstrate a causal relationship between \( \beta \)-blockers and CI in patients with HF.\(^{13,24} \) The prospective, randomized design of our study adds further evidence that \( \beta \)-blockers do not contribute significantly to the pathogenesis of CI in patients with advanced HF. This is especially evident when examining the effect of \( \beta \)-blocker therapy on HR reserve, which represents a better measure of CI in patients with HF on \( \beta \)-blocker therapy, as supported by Witte et al\(^2 \) and Magri et al.\(^1 \) Though our data demonstrates that \( \beta \)-blocker withdrawal increases HR at peak exercise, it does little to reverse CI (percentage HR reserve rose from 51.4 to 62.7%, still markedly below the 80% cutoff limit for CI). In addition, the degree of HR increase after \( \beta \)-blocker cessation in our study is much lower than would be expected if \( \beta \)-blockers were the sole contributor to CI. In a study of healthy subjects, Stoschitzky et al\(^{25} \) demonstrated that administration of metoprolol and carvedilol caused a 16% to 25% reduction in HR during exercise. In contrast, we observed only minimal changes in HR.

It is known that autonomic nervous system activity contributes to the regulation of cardiac output during rest and exercise.\(^{26} \) Vagal reactivation is the principal determinant of HR recovery in the first minute after exercise, and an impaired HR recovery confers an increased risk of death.\(^2 \) It has been shown that vagally mediated HR recovery after exercise is accelerated in athletes and attenuated in patients with chronic HF.\(^{28} \) That \( \beta \)-blocker withdrawal had little effect on HR recovery time suggests that these agents do not interfere with the parasympathetic regulation of HR during exercise in patients with advanced HF.

One proposed mechanism for CI in advanced HF is impaired response to endogenous NE from the constitutive activity of the adrenergic system, leading to \( \beta \)-receptor downregulation.\(^{4,5} \) It is believed that one of the survival benefits conferred by \( \beta \)-blockers in HF is mediated by an increase in both \( \beta \)-receptor density and sensitivity to adrenergic stimulation.\(^{29,30} \) If \( \beta \)-blockers were indeed the dominant cause of CI in patients with advanced HF, then withdrawal of these agents should result in restoration of the normal chronotropic response to endogenous NE. Yet, in our study, cessation of \( \beta \)-blockers did not affect impaired response of HR to endogenous NE during exercise. These findings further support a limited role of these agents in the pathogenesis of CI and exercise intolerance, particularly in advanced HF, which is associated with a greater prevalence of CI.\(^{1,4} \)

It is commonly believed that by reducing HR, \( \beta \)-blockers reduce exercise toleranc. This has led to enthusiasm for rate-responsive pacing in patients receiving cardiac resynchronization therapy and discussions among patients and physicians about whether to reduce \( \beta \)-blockers to ease exercise intolerance. Therefore, perhaps the most intriguing finding in our study is the lack of a clinically relevant difference in exercise capacity between the On-BB and Off-BB conditions despite the differences observed in peak HR during exercise.

Previous studies have shown that as HF progresses, the prevalence of CI increases and the contribution of \( \beta \)-blockers to change in HR decreases.\(^{1,4} \) Similarly, our findings underscore the point that CI exists in advanced HF irrespective of \( \beta \)-blocker therapy.

In this prospective randomized trial, we have further substantiated the hypothesis that impaired chronotropic response during exercise is an intrinsic component of advanced HF that cannot be overcome by acute withdrawal of \( \beta \)-blockers. Whether CI can be overcome by alternate means, including rate-adaptive pacing, as suggested by Tse et al,\(^5 \) remains an intriguing area of research.\(^4 \)
Limitations
Our study was designed as a prospective, randomized, within-subject evaluation of the effect of β-blocker cessation in patients with HF during exercise. Although a significant limitation of our study is the small sample size, that each patient served as his or her own control in the crossover design increased our ability to detect a difference in HR responsiveness during exercise attributable to β-blockade. As with any within-subject crossover design, carryover effects may bias the results; randomization to the order in which the 2 tests were conducted served to counterbalance these effects.

Pharmacokinetics and individual variability in drug response may have implications in the observed effects on HR and exercise tolerance. For example, the partial increase in HR that we observed after β-blocker discontinuation could be the result of an inadequate β-blocker washout period. Though this hypothesis cannot be excluded, the majority of our patients were taking carvedilol with a half-life of 6 to 8 hours. In 26 hours, a complete washout should have occurred, and this period of time is longer than is typically adopted in the clinical setting when β-blocker washout is required.

Last, it has been shown that impaired chronotropic response occurs at a higher frequency in patients with diabetes mellitus, likely as a result of autonomic dysfunction. It is possible that the low prevalence of diabetes mellitus in our study population limits the ability to generalize our findings to this population. However, whether β-blockers differentially affect CI and exercise tolerance specifically in this population has not been well studied.

Conclusion
Our data suggest that acute β-blocker cessation does not restore chronotropic response in advanced HF nor alter the HR response to endogenous NE. β-blockers should be continued in patients with advanced HF; even if severe CI is observed, because they have a negligible role in the pathogenesis of CI and exercise intolerance in this population and confer substantial survival benefits. Our data suggest that β-blockers should also be continued when investigating rate-responsive pacing in patients with advanced congestive heart failure.

Sources of Funding
This study was supported by the National Institutes of Health grant R01HL186845-4.

References
This is the first study to address the effects of β-blocker cessation on both chronotropic incompetence and exercise tolerance in patients with advanced heart failure. We demonstrate that short-term absence of β-blockers does not affect chronotropic incompetence or heart rate response to norepinephrine in these patients. Therefore, we further support the hypothesis that impaired chronotropic response during exercise is an intrinsic component of advanced heart failure that cannot be overcome by acute withdrawal of β-blockers. It is common that patients with advanced heart failure present to their clinician with complaints of exercise intolerance. The clinician must decide whether discontinuing β-blocker therapy offers an improvement in exercise tolerance and, therefore, perhaps quality of life. The clinician often relies on prior experience and anecdotal data to guide this decision. However, discontinuation of β-blockers is problematic given the substantial survival benefit derived from these agents in advanced heart failure. These data may inform the decision as to whether to continue β-blockers in patients with advanced heart failure and chronotropic incompetence for whom rate-responsive therapy is being considered.
Effect of \(\beta\)-Blocker Cessation on Chronotropic Incompetence and Exercise Tolerance in Patients With Advanced Heart Failure

Benjamin J. Hirsh, Andrea Mignatti, A. Reshad Garan, Nir Uriel, Paolo Colombo, Daniel B. Sims and Ulrich P. Jorde

_Circ Heart Fail_. 2012;5:560-565; originally published online August 1, 2012; doi: 10.1161/CIRCHEARTFAILURE.112.967695

_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/5/5/560

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Heart Failure_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Heart Failure_ is online at:
http://circheartfailure.ahajournals.org//subscriptions/