Effect of Beta Blocker Cessation on Chronotropic Incompetence and Exercise Tolerance in Patients with Advanced Heart Failure

Hirsh et al: Beta Blocker Cessation and CI in CHF

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Abstract

**Background**—Chronotropic incompetence (CI) is defined as inability to reach 80% of heart rate reserve (HRR) or 80% of maximally predicted heart rate (MPHR) during exercise. The presence of CI is associated with reduced peak oxygen consumption (pVO$_2$), and rate-responsive pacing therapy is under investigation to improve exercise capacity in HF. However, uncertainty exists as to whether CI and reduced exercised tolerance in HF are attributable to Beta (β)-blockade.

**Methods and Results**—Subjects with HF on long-term β-blocker therapy underwent cardiopulmonary exercise tolerance testing (CPETT) under 2 conditions in random sequence: (1) after a 27 hour ‘washout’ period [Off BB] and (2) 3 hours after β-blocker ingestion [On BB]. Norepinephrine (NE) levels were drawn at rest and at peak exercise. β1-response to NE was assessed using the chronotropic responsiveness index (CRI): ΔHR/ΔlogNE. Nineteen patients with systolic HF (LVEF 22.8±7.7%) were enrolled. Mean age was 49.4±12.3. Average carvedilol equivalent dose was 29.1±17.0 mg daily. Peak HR off/on β-blockers was 62.7±18.7% and 51.4±18.2% HRR (p<0.01) and 79.1±11.0% and 70.3±12.3% MPHR (p<0.01). For the off and on-BB conditions, the Respiratory Exchange Ratio was 1.05±0.06 and 1.05±0.10 (p=0.77), confirming maximal and near identical effort in both conditions. The peak oxygen consumption was 16.6±3.34 and 15.9±3.31 (p=0.03), and the CRI was 19.3±7.2 and 16.2±7.1 (p=0.18).

**Conclusions**—Acute β-blocker cessation does not normalize the chronotropic response to exercise in patients with advanced HF and CI.

**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 (β₁)–receptor downregulation 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 level (ΔHR/ΔlogNE), a measure of β–receptor sensitivity, decreases progressively with the severity of HF.

Nearly half of all HF patients 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 HF patients on β–blockers, controversy exists over whether CI and exercise intolerance are effects of disease progression alone or whether they also can be attributed to pharmacologic β–blockade. Nonetheless, discontinuation of β–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 at the same time administering β–blockers? To further clarify the physiologic consequences of β–blocker therapy in patients with advanced HF, we examined the effects of acute β–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, NYHA class II-IV, on β-blocker therapy (Bisoprolol, Carvedilol, or Metoprolol) for ≥ 3 months referred for cardiopulmonary exercise tolerance testing (CPETT) testing were screened. All patients were followed at the Columbia University Medical Center Heart Failure Center by heart failure specialists. 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 (e.g., severe obstructive pulmonary disease or severe osteoarthritis). Chronotropic incompetence was not a factor in enrollment. Carvedilol equivalent dose was calculated for Bisoprolol and Metoprolol-treated patients based on the equivalence ratios established by the MERIT-HF study.16

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, as Carvedilol, Metoprolol, and Bisoprolol reach a peak concentration between 2-4 hours.17,18 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. 11 patients were randomized to the On-BB condition first and 12 patients were randomized to the Off-BB condition first.

EXERCISE TESTING

Resting HR was obtained after 30 min of rest in a quiet, temperature-controlled room. Peak oxygen consumption (pVO2 [mL/kg/min]) 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 prior to 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.¹⁹

HR and electrocardiogram 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 following 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 (RER) was ≥1.0. Chronotropic incompetence was defined using the %HRR formula and %MPHR formula, with a cutoff of < 80% for both measures.²²⁰ The anaerobic threshold (AT) was identified by V-slope method.²¹ Oxygen pulse was calculated by dividing pVO2 by the HR at the time pVO2 was achieved, expressed as milliliters per heart beat.¹⁹ The chronotropic responsiveness index (CRI)
was calculated using the following formula: \( \frac{\text{peak HR} - \text{baseline HR}}{\log(\text{peak NE} - \text{baseline NE})} \).9-11

MEASUREMENT OF NOREPINEPHRINE
Following 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 cm\(^3\) of venous blood was collected in EDTA vials: 15 cm\(^3\) after 30 minutes of rest and an additional 15 cm\(^3\) during peak exercise. Samples were stored on ice until centrifugation and then frozen immediately at \(-80^\circ\text{C}\). Norepinephrine was measured using high performance liquid chromatography.1,22

STATISTICAL ANALYSIS
All analyses were performed using SPSS software. Continuous variables are expressed as mean \(\pm\) standard deviation. 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 two-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 on a stable, maximally-tolerated \(\beta\)-blocker therapy for > 3 months. Only 2 of the subjects had a change in the \(\beta\)-blocker dose within the 3 months prior to CPETT. In 1 of the subjects, Carvedilol was
changed from 3.125mg BID to 6.25mg BID at 2 months prior to CPETT. In the other subject, Carvedilol was changed from 6.25mg BID to 12.5mg BID at 6 weeks prior to 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: one 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 non-parametric testing yielded similar results. In each condition, patients had near identical RER and exercise time. In the On-BB condition, patients had a lower resting HR, a smaller change in HR, a lower HR at AT, 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 the VO2 at AT and only a small difference in the 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 %MPHR and %HRR was higher after holding β–blockers, more than 75% of patients in each condition had a value below the <80% cutoff value for establishing chronotropic incompetence (Figure 3). The HR and BP response to orthostasis differed between conditions (Figure 4). HR recovery at 1 minute following 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 CRI between conditions.
(Table 2). Change in HR correlated with pVO₂ in the On-BB (R=0.60, p=0.01) and Off-BB condition (R=0.49, p=0.03) (Figures 5A and 5B).

DISCUSSION

We examined whether acute cessation of β–blockade in patients with advanced HF affects chronotropic incompetence, 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 β–blocker cessation on CI in patients with advanced HF chronically treated with β–blockers, and our principal findings are as follows: First, although withdrawal of β–blockers increases peak HR during exercise, it does not normalize the chronotropic response, and CI persists. Second, efficiency decreases after withdrawal of β–blockade as evidenced by a decreased oxygen pulse. Third, although β–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. Lastly, the impaired HR response to increasing NE levels, i.e., the CRI, during exercise is not affected by acute β–blocker withdrawal in HF patients on long-term β–blocker therapy.

Several prior studies, albeit mostly of cross-sectional, retrospective nature in relatively healthier patient populations, have failed to demonstrate a causal relationship between β–blockers and CI in HF patients. The prospective, randomized design of our study adds further evidence that β–blockers do not contribute significantly to the pathogenesis of CI in patients with advanced HF. This is especially evident when examining the effect of β–blocker therapy on HRR, which represents a better measure of CI in HF patients on β–blocker therapy as supported by Witte et al and Magri et al. Though our data demonstrates that β–blocker withdrawal increases HR at
peak exercise, it does little to reverse CI (%HRR rose from 51.4% to 62.7%, still markedly less than 80% cutoff limit for CI). Additionally, the degree of HR increase following β–blocker cessation in our study is much lower than would be expected if β–blockers were the sole contributor to CI. In a study on healthy subjects, Stoschitzky et al demonstrated that administration of metoprolol and carvedilol caused a 16-25% reduction in HR during exercise.25 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.27 It has been shown that vagally-mediated HR recovery after exercise is accelerated in athletes and attenuated in patients with chronic HF.28 That β–blocker withdrawal had little effect on HR recovery times suggests that these agents do not interfere with the parasympathetic regulation of HR in patients with advanced HF during exercise.

One proposed mechanism for CI in advanced HF is impaired response to endogenous NE from constitutive activity of the adrenergic system leading to β–receptor downregulation.4,9 It is believed that one of the survival benefits conferred by β–blockers in HF is mediated by an increase in both β–receptor density and sensitivity to adrenergic stimulation.29,30 If β–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 β–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 heart rate, β-blockers reduce exercise tolerance. This has led to an enthusiasm for rate-responsive pacing in CRT patients and discussions amongst patients and physicians about whether to reduce β-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 β-blockers to change in HR decreases.1,3,4 Similarly, our findings underscore the point that CI exists in advanced HF irrespective of β-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 β-blockers. Whether CI can be overcome by alternate means including rate-adaptive pacing, as suggested by Tse et al, remains an intriguing area of research.14,15

LIMITATIONS

Our study was designed as a prospective, randomized within-subject evaluation of the effect of β-blocker cessation in HF patients during exercise. Though a significant limitation of our study
is the small sample size, the fact that each patient served as his or her own control in the cross-over design increased our ability to detect a difference in HR-responsiveness during exercise attributable to β-blockade. As with any within-subject cross-over design, carryover effects may bias the results; randomization to the order in which the two 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 6-8 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.

Lastly, it has been shown that impaired chronotropic response occurs at a higher frequency in patients with diabetes, 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 suggests 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, as they have a negligible role in the pathogenesis of CI and exercise intolerance in this population and confer substantial survival benefits. Our data suggests that β-blockers should also be continued when investigating rate-responsive pacing in patients with advanced CHF.

SOURCES OF FUNDING

NIH R01HL186845-4

DISCLOSURES

None.

REFERENCES

9. Samejima H, Omiya K, Uno M. Relationship between impaired chronotropic response,


<table>
<thead>
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<th>Variable</th>
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<td>Male Sex</td>
<td>12 (63.2)</td>
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<tr>
<td>Height (in)</td>
<td>66.6±4.3</td>
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<tr>
<td>Weight (lbs)</td>
<td>192.5±48.3</td>
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<td>LVEF</td>
<td>22.8±7.7</td>
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<td>5 (26.3)</td>
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<tr>
<td>Carvedilol</td>
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<tr>
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<td>Digoxin</td>
<td>5 (26.3)</td>
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<tr>
<td>Statin</td>
<td>12 (63.2)</td>
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LVEF, left ventricular ejection fraction; 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 formula\(^23\); ACE, Angiotensin Converting Enzyme.
<table>
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<tr>
<th>Outcome Variables</th>
<th>On-BB Mean±SD (N=19)</th>
<th>Off-BB Mean±SD (N=19)</th>
<th>P-Values</th>
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<td>Resting HR</td>
<td>66.1±13.4</td>
<td>72.3±12.3</td>
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<td>Supine SBP</td>
<td>105.3±9.1</td>
<td>112.9±16.6</td>
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<td>1 min standing SBP</td>
<td>102.2±10.2</td>
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<tr>
<td>1 min standing HR</td>
<td>72.1±12.7</td>
<td>77.7±13.5</td>
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<tr>
<td>Peak HR</td>
<td>120.1±23.7</td>
<td>134.8±22.0</td>
<td>&lt;0.01</td>
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<td>ΔHR</td>
<td>54.0±22.6</td>
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<td>15.7±2.1</td>
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<tr>
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<td>%HRR</td>
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<td>62.7±18.7</td>
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<tr>
<td>%MPHR</td>
<td>70.3±12.3</td>
<td>79.1±11.0</td>
<td>&lt;0.01</td>
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<tr>
<td>O₂ Pulse (mL/beat)</td>
<td>12.3±3.5</td>
<td>11.4±3.0</td>
<td>0.04</td>
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<tr>
<td>NE pre (pg/mL)</td>
<td>2508.2±1111.5</td>
<td>2082.3±936.0</td>
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<td>NE post (pg/mL)</td>
<td>4643.8±2571.8</td>
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<td>CRI</td>
<td>16.2±7.1</td>
<td>19.3±7.2</td>
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HR, heart rate; SBP, systolic blood pressure; ΔHR, difference between peak and resting HR; HR Recovery (HRR), difference between peak HR and HR one minute following exercise.
completion; AT, anaerobic threshold; O$_2$, Oxygen; NE pre and post, NE levels at rest and at peak exercise; $\Delta$NE, difference between resting and peak NE; CRI, chronotropic responsiveness index; MPHR, maximally predicted heart rate.
**FIGURE LEGENDS**

**Figure 1.** Testing Profile.

**Figure 2.** HR as a function of work rate via a modified Naughton Protocol. In the On-BB condition, HR is significantly decreased compared to the Off-BB condition at each time point. ^p<0.05, *p<0.001, **p<0.00001, ANOVA with repeated measures.

**Figure 3.** Percentile of HRR by quartile. Cut-off of <80% defines chronotropic incompetence.

**Figure 4.** Change in HR in both supine and standing position.

**Figures 5A and B.** Correlation between change in HR and peak oxygen consumption in the On-BB condition (R=0.60, p=0.01) and Off-BB condition (R=0.49, p=0.03).
HF Patients Enrolled and Randomized to the Order of Testing Conditions
N=23

On BB Condition
N=23

Off BB Condition
N=23

Excluded from Final Analysis
- Pacing Observed (n=2)
- Patient Did Not Return for Second Visit (n=1)
- Cuff-leak in Mouthpiece Observed (n=1)

HF Patients Included in Final Analysis
N=19
Figure 4

HR and Orthostatic load

\[
\begin{align*}
\text{supine HR} & \quad 64 \quad 66 \quad 68 \quad 70 \quad 72 \\
1 \text{ min standing HR} & \quad 72 \quad 77
\end{align*}
\]

- ON BB
- OFF BB

\{ p<0.01 \}
Figures 5A and 5B
Effect of Beta Blocker Cessation on Chronotropic Incompetence and Exercise Tolerance in Patients with Advanced Heart Failure
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