The Effect of Long-Term β-Adrenergic Receptor Blockade on the Oxygen Delivery and Extraction Relationship in Patients With Coronary Artery Disease

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PURPOSE: We evaluated the effects of long-term β-blocker treatment on the balance between oxygen delivery and extraction at peak oxygen uptake (VO₂) and at target heart rate training (anaerobic threshold).

METHODS: Fifteen patients with coronary artery disease performed paired peak cardiopulmonary and submaximal exercise tests on a cycle ergometer with and without atenolol treatment. Thirty minutes following the submaximal tests, participants pedaled 10 minutes at a workload corresponding to that of the anaerobic threshold attained. Arterial oxygen was defined from echocardiography and venous oxygen content.

RESULTS: At rest, stroke volume, heart rate, and cardiac output were lower (P < .05), whereas arteriovenous oxygen difference [(a – v)O₂] was higher with the use of atenolol (P < .05). At peak exercise, heart rate, lactate, and systolic blood pressure were lower (P < .05), whereas (a – v)O₂ was higher (P < .05) with the use of atenolol. At anaerobic threshold, stroke volume, heart rate, cardiac output, and systolic blood pressure were lower (P < .05), whereas (a – v)O₂ was higher (P < .05) with the use of atenolol. Absolute VO₂ and workload during maximal (P = .67 and P = .49, respectively) and submaximal (P = .13 and P = .44, respectively) exercises were similar between conditions.

CONCLUSIONS: Results demonstrate that atenolol treatment in patients with coronary artery disease does not alter VO₂ and workload at the anaerobic threshold and peak exercise because of an increase in oxygen extraction and stroke volume in the face of reduced heart rate. These findings indicate that with long-term β-adrenergic receptor blockade, there is interplay between oxygen delivery and extraction, suggesting a link between cardiac hemodynamic responses and skeletal muscle metabolic adaptations.

KEY WORDS
- cardiac output
- Fick equation
- heart rate
- oxygen extraction
- stroke volume

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Coronary artery disease (CAD) decreases physical performance and maximal oxygen uptake (VO₂). This may be due to a reduction in oxygen delivery to the working muscle and reduced arteriovenous oxygen difference [(a – v)O₂] at maximal effort. Incremental exercise is characterized by the exposure of participants to a high degree of load that may alter left ventricular contractility and function, causing reduction
in oxygen delivery to the working muscle. Because the metabolic demand during incremental exercise is increased over time to maximum values, patients with CAD may maintain their energy supply because of the balance between oxygen delivery and oxygen extraction. Drugs that selectively block adrenergic activity in cardiac and vascular smooth-muscle cells play an important role in the treatment of patients with CAD and/or essential hypertension. These drugs regulate heart rate, myocardial contraction force, vascular resistance, and energy expenditure.

Although there are studies on left ventricular function and metabolic cost during prolonged dynamic exercise and maximal graded dynamic exercise testing in patients with CAD, few data are available regarding the effects of CAD and long-term β-blocker treatment on the balance between oxygen delivery and extraction at peak VO₂ and at target heart rate training (anaerobic threshold). Therefore, the purpose of this study was to observe the influence of long-term β-adrenergic blockade on oxygen delivery and extraction at the anaerobic threshold and at peak exercise with and without β-blockers in patients with CAD.

### METHODS

Fifteen men (aged 62 ± 6 years, 86.4 ± 11 kg) with CAD volunteered to participate in this study. A written consent form was obtained from all participants after they had been fully informed of the details and possible discomforts associated with the experimental protocol. The study was approved by the Clinical Science Center committee on human subjects that complies with the Declaration of Helsinki. All patients had prior myocardial infarction or CAD, documented within 1 year of the study by clinical and electrocardiography (ECG) criteria and cardiac catheterization that revealed single-vessel disease without wall motion abnormalities. Patients took only atenolol as their β-adrenergic blocking agent (4 patients had been taking 50 mg · d⁻¹ and 11 patients taking 25 mg · d⁻¹) for at least 3 months before testing. They were asked to withdraw from the atenolol treatment 1 week before testing to enable sufficient washout. Before testing without atenolol, a 1-week period of washout occurred in all patients. Patients were not included in this study if they had mitral regurgitation, rhythm abnormalities, systemic hypertension or left ventricular hypertrophy, history of autoimmunity, cancer, diabetes, and other endocrinopathy, renal failure, recent infection, or recent hospitalization. All patients had been active participants in a supervised aerobic cardiac rehabilitation program (without resistive training) for at least 12 months and had attained a functional capacity of 10 ± 1 METs (1 MET = metabolic equivalent).

### Procedures

Five testing sessions were conducted for all participants, each session lasting approximately 1 hour with at least 1 day and no more than 3 days of rest between each trial. Tests were performed at the same hour of the day to control diurnal variation of heart rate and blood pressure. The first session was devoted to habituating the participants to the cycle ergometry and clarifying the specific protocols used in this study. During the second through fifth testing sessions, participants underwent a graded maximal or submaximal exercise test on a mechanical weight-adjusted Monark cycle ergometer (Model 818, Monark, Sweden). Participants were secured by torso straps to the wall while cycling. This was done to minimize movement of the upper body and facilitate auscultation of blood pressure and echocardiography measurements during submaximal and maximal exercises. During the second and third sessions, participants underwent peak cardiopulmonary exercise stress tests, with and without atenolol treatment. Following warm-up, all patients performed the cardiopulmonary exercise stress test on a cycle ergometer. According to the guidelines of the American College of Sports Medicine, termination of the cardiopulmonary stress test was determined by the following criteria: (a) leveling of or no further increase in VO₂ with increased workload, (b) attainment of the age-predicted maximum heart rate (as calculated on the basis of Karvonen equation), (c) respiratory exchange ratio greater than 1.1, or (d) when the participant could no longer continue at the predetermined pace. All patients terminated the test with the achievement of peak VO₂. The order of the second and third testing sessions was counterbalanced among participants. During the fourth and fifth sessions, participants underwent submaximal tests to define anaerobic threshold, once with and once without atenolol treatment. Thirty minutes following the submaximal tests, participants were asked to pedal 10 minutes at a steady state pace, applying a workload corresponding to that of the anaerobic threshold attained.

### Measurements

Oxygen uptake was determined breath by breath, utilizing the Medical Graphics (St Paul, Minnesota) metabolic cart. The metabolic cart was calibrated before each test with known primary standard quality gases. Following warm-up, participants pedaled against an initial workload of 100 W, which was increased by 25 W every minute until the participant
could no longer continue at the predetermined pace. Cardiac output was measured at peak exercise by means of echocardiography measurements. Heart rate and ECG measurements were monitored continuously, using a Burdick Eclipse 400 3-channel, 12-lead ECG recorder system, and an oscilloscope. Five-second recordings were obtained at rest and at the end of each minute throughout the tests. Blood pressure measurements were taken at rest and during the last 30 seconds of each stage of the tests. Each testing session was supervised by a physician. To determine the venous oxygen content, blood samples were drawn from the antecubital brachial vein, 3 minutes following the maximal, submaximal, and 10-minute exercises. Oxygen saturation and hemoglobin concentration were measured independently in each blood sample (using IOSM3 hemoximeter, Radiometer).

**Lactate Measurements**

A 25 µL of fingertip blood sample was taken at rest and at the end of the third-minute postmaximal, submaximal, and the 10-minute exercises for determination of lactate response. Lactate sampling was done 3 minutes following exercise to allow equilibration in the concentrations of lactate between muscles and blood as suggested previously. The work rate corresponding to 4 mmol of lactate was calculated according to the Karvonen equation. The anaerobic threshold was determined as the workload corresponding to the blood lactate level of 4 mmol · L⁻¹ during an incremental load test according to the recommendations of Mader and Heck. The sample was immediately transferred to a microtube containing 100 µL of 7% perchloric acid. The tubes were centrifuged after standing at least 1 hour. Twenty-microliter aliquots of the supernatant were subsequently used for lactate analysis on the Analox LM3 analyzer (Analox Instruments, England; Reagent Kit # GMRD-071).

**Echocardiography Data**

Two-dimensional echocardiography and M-mode echocardiography were performed both at rest and at peak exercise, utilizing the Vingmed 725 Sonotron and a Sony recorder equipped with 2- and 3-MHz transducers. The diameter of the aorta was determined by 2-dimensionally directed M-mode echocardiography. The left atrium size was measured from the parasternal long-axis view. At rest, left ventricular end-diastolic and end-systolic diameters and intra-ventricular septum and left ventricular posterior wall thicknesses were measured from the parasternal long- and short-axis views and from 4- and 5-chamber views, just below the mitral valve level, according to the recommendations of the American Society of Echocardiography. Because of the short time available for measurements at peak exercise, left ventricular volumes and ejection fraction were determined using Simpson’s rule from the apical 4-chamber view. All echocardiography studies were performed with the participants in the sitting position at rest and at peak aerobic and anaerobic efforts. The probe was hand held and directed to a marked point from which the resting data were obtained. The beam was directed to the aortic valve outflow tract in the 5-chamber view, or from the supersternal approach in those participants for whom adequate imaging of 5-chamber or parasternal long-axis views was not obtained. To assess the objectivity of the echocardiography readings, 2 independent experts evaluated all recordings. A high correlation (r = 0.89) was found for interobserver reliability.

At rest and during exercise, hemodynamic variables were computed as follows: Stroke volume was the difference between left ventricular end-diastolic volume and end-systolic volume. Cardiac output was determined as the product of heart rate and stroke volume. Venous oxygen content (mL O₂ · dL⁻¹) was calculated from measured oxygen saturation and hemoglobin concentration multiplied by 1.34 mL of oxygen. Arterial oxygen content was calculated utilizing the Fick equation, in which Vo₂ = heart rate × stroke volume × (a − v)O₂. Therefore, (a − v)O₂ was calculated by using the measured Vo₂, cardiac output, and venous oxygen content. Work capacity in METs was determined by dividing peak Vo₂ achieved with resting Vo₂.

**Statistical Analysis**

Data are reported as mean ± SD. A 2-way analysis of variance with repeated measures was performed for multiple comparisons; a post-hoc analysis was performed by using the Tukey 2 multiple comparison test. The level of significance was set at P < .05.

**RESULTS**

All the participants completed the study without any difficulties or clinical abnormalities, including ECG irregularities. At rest (Table 1), values of Vo₂, lactate, diastolic blood pressure, Borg Scale, and workload did not differ between conditions. However, as shown in Figure 1, stroke volume, heart rate, and cardiac output were lower (P < .05) whereas (a − v)O₂ was higher with the use of atenolol (P < .05). All hemodynamic variables except for diastolic blood pressure increased significantly (P < .05) from rest to submaximal and maximal exercise. Table 2 compares values of hemodynamic variables achieved at peak exercise with and without the use of atenolol. It reveals that heart rate, lactate level, and systolic blood pressure were lower (P < .05), whereas (a − v)O₂
was higher ($P < .05$) with the use of atenolol. At the anaerobic threshold (Table 1 and Fig 1), stroke volume, heart rate, cardiac output, and systolic blood pressure level were lower ($P < .05$), whereas $(a - v)O_2$ was higher ($P < .05$) with the use of atenolol. At peak maximal and submaximal exercises, values of VO$_2$ ($P = .67$ and $P = .13$, respectively), diastolic blood pressure ($P = .54$ and $P = .60$, respectively), Borg Scale ($P = .14$ and $P = .07$, respectively), and workload ($P = .49$ and $P = .44$, respectively) did not differ significantly between conditions.

**DISCUSSION**

The study showed that in patients with CAD, long-term $\beta$-adrenergic receptor blockade does not alter VO$_2$ and workload during submaximal and maximal aerobic exercise. Despite the changes in cardiac output and circulatory responses to exercise and in the face of reduced heart rate produced by $\beta$-adrenergic blockade, the preserved VO$_2$ of the working muscles

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**Table 1 • HEMODYNAMIC VARIABLES ATTAINED AT REST AND AT ANAEROBIC THRESHOLD WITH AND WITHOUT THE USE OF ATENOLOL (MEAN ± SD)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>Anaerobic threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atenolol</td>
<td>No drug</td>
</tr>
<tr>
<td></td>
<td>3.1 ± 0.45</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td>VO$_2$, mL·kg$^{-1}$·min$^{-1}$</td>
<td>14.4 ± 1.3</td>
<td>14.9 ± 1.5</td>
</tr>
<tr>
<td>Cardiac output, L·min$^{-1}$</td>
<td>4.2 ± 1.4</td>
<td>5.0 ± 1.8</td>
</tr>
<tr>
<td>Blood lactate, mmol·L$^{-1}$</td>
<td>1.44 ± 0.3</td>
<td>1.48 ± 0.3</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>118.5 ± 6.7</td>
<td>125 ± 7.1</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>76 ± 4.2</td>
<td>78 ± 3.5</td>
</tr>
<tr>
<td>Borg Scale</td>
<td>13.7 ± 1.3</td>
<td>14.6 ± 1.0</td>
</tr>
<tr>
<td>Workload, W</td>
<td>79.7 ± 1.8</td>
<td>81.3 ± 2.5</td>
</tr>
</tbody>
</table>

**Table 2 • HEMODYNAMIC VARIABLES ATTAINED AT PEAK EXERCISE WITH AND WITHOUT THE USE OF ATENOLOL (MEAN ± SD)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>Anaerobic threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atenolol</td>
<td>No drug</td>
</tr>
<tr>
<td></td>
<td>116 ± 13</td>
<td>117 ± 17</td>
</tr>
<tr>
<td>(a - v)O$_2$, O$_2$ mL·L$^{-1}$</td>
<td>132.0 ± 3.1</td>
<td>127.0 ± 4.3</td>
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<tr>
<td>VO$_2$, mL·kg$^{-1}$·min$^{-1}$</td>
<td>30.1 ± 3.0</td>
<td>29.7 ± 2.7</td>
</tr>
<tr>
<td>Cardiac output, L·min$^{-1}$</td>
<td>19.7 ± 1.3</td>
<td>20.2 ± 1.7</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>136.7 ± 9.9</td>
<td>129.3 ± 9.7</td>
</tr>
<tr>
<td>Heart rate, beats·min$^{-1}$</td>
<td>144.1 ± 9.5</td>
<td>156.2 ± 8.6</td>
</tr>
<tr>
<td>Blood lactate, mmol·L$^{-1}$</td>
<td>7.2 ± 0.9</td>
<td>8.1 ± 0.7</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>167.5 ± 16.0</td>
<td>180.0 ± 13.5</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>78.0 ± 6.2</td>
<td>79.0 ± 6.1</td>
</tr>
<tr>
<td>Borg Scale</td>
<td>18.9 ± 0.7</td>
<td>19.4 ± 0.5</td>
</tr>
<tr>
<td>Workload, W</td>
<td>176.6 ± 12.5</td>
<td>175.7 ± 11.7</td>
</tr>
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</table>

**Abbreviations:** BP, blood pressure; VO$_2$, oxygen uptake.

*Significant differences between conditions at rest.

*Significant differences between conditions during exercise.
may be attributed to an increase in oxygen extraction and stroke volume. These findings suggest that in patients with CAD undergoing long-term β-blocker treatment, VO₂ during prolonged dynamic exercise is maintained over time because of a balance between oxygen delivery and extraction.

At peak cardiopulmonary stress, oxygen extraction was not the factor that maintained VO₂ in patients who exercised without atenolol. Instead, it was maintained because of a significant increase in heart rate and to a lesser extent in stroke volume. In contrast to previous reports, with long-term β-adrenergic receptor blockade, a significant increase in oxygen extraction and stroke volume occurred, which compensated for the lower heart rate and cardiac output.

We showed that long-term atenolol treatment does not cause any reduction in VO₂ and workload at anaerobic threshold and at peak exercise in patients with CAD. We are aware of the disagreement between our findings in patients showing similar Borg Scale values between conditions and the findings reported by Wolfe et al13 in healthy individuals. However, it should be noted that in the latter study, the difference between conditions in perceived intensity was evidenced only in high altitudes, whereas at sea level, there was no difference. Importantly, the results found here in patients with CAD may not apply to healthy individuals. In line with this concept, in patients with hypertension, Brion et al14 found that long-term administration of cardioselective β-adrenergic receptor blockade did not have an impact on maximal exercise capacity. In other studies as well, no significant change occurred with regard to the relationship of VO₂ and workload at peak exercise performed with and without β-blockade, further supporting our results.15,16

Our patients who were taking atenolol increased their stroke volume at peak exercise. We hypothesize that this response is most probably because of the lesser increase in mean arterial blood pressure. This response, however, is different from that reported in a previous study, which found that during strenuous exercise, well-trained healthy young adult participants did not increase their stroke volumes.4 Moreover, in healthy individuals, β-blockade can impair contractility. In this study, left ventricular function at peak effort did not differ between conditions. The mechanics of ventricular contraction is a concept involving force, length, velocity, and time,17 and independent of preload.4 At peak exercise with atenolol treatment, the increase in stroke volume was most likely because of the relatively lower afterload opposing left ventricular ejection.18 Such a response may reflect both an increase in inotropism and a decrease in systemic vascular resistance during exercise because of the influence of β-adrenergic receptor blocking.19 However, the lower heart rate with β-blockade may increase diastolic filling time, which may increase preload and thereby augment stroke volume via the Frank-Starling mechanism. The observed lower stroke volume and higher heart rate at peak exercise without β-blockade may be at least partially because of the smaller reduction in total peripheral resistance, which can probably be attributed to the greater concentrations of vasoactive substances owing to tissue hypoxia and acidosis.20 In addition, it may be that the lower stroke volume is a result of reduced left ventricular filling time in the face of higher heart rates.

There were no significant differences in VO₂ or workload at the anaerobic threshold, with and without atenolol treatment. However, measurements of left ventricular function revealed that despite the reduced heart rate and cardiac output when taking atenolol, VO₂ was compensated by an increase in oxygen extraction only and not by an increase in stroke volume as well, as previously suggested.12 The observed lower stroke volume and heart rate during the anaerobic threshold bout with atenolol (Fig 1) may be due to reduced inotropism following the administration of β-adrenergic blockers. Without atenolol treatment, VO₂ during the submaximal test was not maintained by oxygen extraction. Instead, as previously suggested, it was maintained as a result of the significant increases in heart rate and stroke volume (Fig 1) and thus of cardiac output.12

In this study, patients were well trained and participated in an aerobic cardiac rehabilitation program to increase their skeletal muscle oxidative capacity.21 Exercise-induced biochemical adaptations of skeletal muscles might be related to increases in muscle mitochondria concentration and capillary network. The preserved VO₂ and the relatively high oxygen extraction in our participants undergoing β-adrenergic receptor blockade suggest that intrinsic mitochondrial function and regulation were not altered by the use of atenolol. It should be noted, however, that in some reports dealing with the effect of β-blocker therapy on maximal exercise performance in active hypertensive patients, a reduction in maximal VO₂ has been demonstrated.22,23

### CLINICAL IMPLICATIONS

In cardiac patients undergoing long-term β-adrenergic receptor blockade, there is an interplay between oxygen delivery and extraction, so that the overall VO₂ of the working muscles while exercising is not affected. These findings suggest a link between physiologic
hemodynamic responses and skeletal muscle metabolic adaptations. Thus, patients taking atenolol can partially compensate for lower cardiac output by increasing oxygen extraction. Aerobic training aimed at improved peak VO₂ and physical performance play an important role in cardiac rehabilitation programs. Our findings support the concept that for patients participating in these programs who are undergoing long-term β-blockade, the anaerobic threshold may have a substantial impact for training prescription with regard to the upper limit of their exercise training intensity. The fact that these patients are able to increase their oxygen extraction and stroke volume in the face of reduced heart rate suggests that they may be trained at higher heart rates and workloads.

References