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*Full Length Research Paper*

# The role of beta 2 – agonists in improving exercise response in hypertensive patients

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**The hypothesis that celiprolol, a β-1 adrenoceptor antagonist with the ancillary property of β-2 mediated vasodilation, would increase blood flow to active muscles during exercise and result in less impairment of exercise performance, compared with the β-1 antagonist atenolol was tested. After an initial 3 weeks washout phase, 11 untrained hypertensive men participated in a 6 week crossover study of the two drugs. Each treatment phase was followed by a 3 week placebo phase. Resting forearm and calf vascular resistance measured by venous occlusion plethysmography and submaximal and maximal bicycle ergometer exercise responses were evaluated at the end of each treatment and placebo phase. Celiprolol significantly decreased resting forearm and calf vascular resistance whereas atenolol had no significant effect. Neither β-blocker significantly affected submaximal exercise oxygen uptake, rate of perceived exertion, minute ventilation, or respiratory exchange ratio. Both β-blockers significantly and similarly decreased peak oxygen uptake; celiprolol 23.9 ±1.7, atenolol 24.9 ± 1.7, placebo 27.3 ± 1.3 ml/kg/min. These findings suggest that during exercise while on β-blockade, other factors such as sympathetic vasoconstriction or local metabolic vasodilation may override β-2-mediated vasodilation. Thus, the addition of β-2 agonist to β-1 antagonism decreases resting vascular resistance, but offers no advantage over conventional β-1 blockade therapy during exercise.**

**Key words:** Celiprolol, atenolol, oxygen uptake, venous occlusion plethysmography, bicycle ergometer, β-blocker, blood flow, vascular resistance.

## INTRODUCTION

The primary hemodynamic disturbance in individuals with established hypertension is elevated peripheral resistance with normal or low cardiac output (Folklow, 1982; Freis, 1960). During exercise, peripheral vascular resistance decreases but not to the same extent as in individuals who are normotensive cardiac output is generally subnormal during exercise (Lund-Johansen, 1980).

Although treatment of hypertension with β-adrenergic blocking agents usually effectively lowers blood pressure (BP), this class of drug does not improve the hemodynamic profile of these patients either at rest or during exercise. Patients frequently complain of cold extremities, bronchoconstriction, and generalized fatigue. In addition, maximal exercise capacity is typically reduced by 15 to 20% on β-blocking agents (Kalser et al.,

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1986; Lund-Johansen, 1987; Petersen et al., 1983; Kokkinos et al., 2006). It has been postulated that a reduced cardiac output and increased total peripheral resistance could contribute to inadequate blood flow to the active muscles and early onset of fatigue during exercise.

Celiprolol, a relatively β-1 receptor antagonist, has ancillary vasodilatory activity due to β-2 receptor stimulation (Wolf etal., 1985). Also, less resting bradycardia has been observed with celiprolol administration, suggesting partial intrinsic sympathomimetic activity (Wheeldon et al., 1992).

This study was designed to test the hypothesis that celiprolol, compared with the β-1 receptor antagonist atenolol, would allow more blood flow to the active muscles and produce less slowing of heart rate during exercise, thus resulting in less submaximal fatigue and a higher peak exercise capacity.

## METHODOLOGY

### Research design

The study was double-blind randomized crossover comparison of celiprolol and atenolol. It began with a 3-weeks placebo washout phase followed by randomization to one of the β-blockers for 6 weeks. Patients were initially started on either 200 mg celiprolol QD or 50 mg atenolol QD and escalated to 400 mg QD and 100 mg QD, respectively, at week 4 if their supine diastolic BP was greater than 90 mmHg. After an intervening 3-week placebo phase, subjects were crossed over to the alternate β-blocker. A final 3-weeks placebo phase concluded the study.

### Subjects

Eleven untrained males aged 40.5 ± 8.6 years participated in the study. Their mean body mass index was 27.8 ± 2.9, untreated supine BP was 141 ± 10/98 ±6 mmHg, and peak oxygen uptake during the initial placebo washout phase was 26.5 ± 3.6 ml/kg/min. No other medication that would affect BP or hemodynamic measurements were allowed during the 21-week study, and subjects were asked wet to change their arrearage level of physical activity. Subjects reported to all visits after an overnight fast. Written informed consent was obtained prior to participation. The study was approved by the University Human Subjects Committee.

### Protocol

During the initial placebo phase subjects were introduced to the technique of venous occlusion plethysmography for the measurement of peripheral blood flow (BF) and performed peaksub maximal bicycle tests. No data from the phase were analyzed except for the peak exercise capacity data. The absolute workloads in Watts (W) to be used for all sub maximal tests during the study were calculated from 25, 50, and 75% of the peak W level obtained at week 2 of this initial placebo phase.

During the treatment phases, subjects reported to the laboratory at 11.00 am at week 5 for the determination of peak bicycle exercise capacity 5 h after taking the study pill. At week 6, subjects reported to the lab at 8.00 am. Resting BP in various positions were measured first, resting and sub-maximal blood flow measurements were made at 9.00 am and submaximal bicycle exercise was performed at 11.00 am, again 5 h after taking the study pill. The same procedures were performed at weeks 2 and 3 of the middle and final placebo phases that were performed at weeks 5 and 6, respectively, of the treatment phases.

### Procedures

#### *Peripheral blood flow*

Forearm blood flow (FBF) and calf blood flow (CBF) were measured by venous occlusion plethysmography (Whitney, 1953) with the subject in a semi recumbent position. The mean of three auscultatory BPs obtained during the resting BF measurement was used to calculate mean arterial pressure (MAP) from diastolic pressure + 1/3 (systolic blood pressure). Regional vascular resistance was calculated from MAP/BF, CBF was also measured after 2 min of unresisted ankle flexion at the rate of one 30° extension and flexion every 2 s. The calf exercise was performed in the semi-recumbent position with the strain gage in place which allowed for immediate blood flow measurement upon cessation of rhythmic ankle flexion. The BP obtained immediately prior to stopping exercise and the first CBF measured after exercise were used to calculate isolated calf exercise vascular resistance.

#### *Peak bicycle exercise*

Bicycle exercise was performed to maximal effort on a Siemens Ergomed 840 ergometer controlled by a Burdick M330d controller using a ramping protocol of 15 W/min. The test was terminated when the subjects could no longer maintain their chosen pedal speed and the highest Watts level attained was used as subjects maximum power output. BPs and heart rates (HR) were measured every minute during exercise. The subjects were asked to indicate their rating of perceived exertion (RPE) by pointing to a number on the Borg RPE scale every 2 min during the test. Respiratory variables were measured continuously using a system 2000 metabolic measurement Cart (Medical Graphics Corporation).

#### *Submaximal bicycle exercise*

Subjects cycled continuously for 2 min of free-wheel warm up, three 8-min stages at 25, 50, and 75% of their peak Watts level from the initial placebo phase and 2 min of cool down. HR, BP, and RPE were obtained every 2 min and respiratory variables were measured continuously.

### Data analysis

Conventional descriptive statistics were used for subject characteristics; values are presented as mean ± standard deviation (SD), stepwise student's paired t-test were used to detect differences in means during treatment phases: (1) two tailed t-test were used to detect differences between the two placebo phases: postceliprolol placebo phase (that following the celiprolol treatment phase) and postatenolol placebo phase (that following the atenolol treatment phase), (2) one tailed t-test were used to detect a significant effect from celiprolol compared with the postceliprolol placebo phase and a significant effect from atenolol compared to the postatenolol placebo phase; the Bonferoni correction for multiple comparisons was used at this step, (3) two-tailed t-tests were used to detect differences between the two treatment phases (celiprolol vs. atenolol), linear regression analysis was performed by the method of least squares. Values of $P < 0.05$ were considered

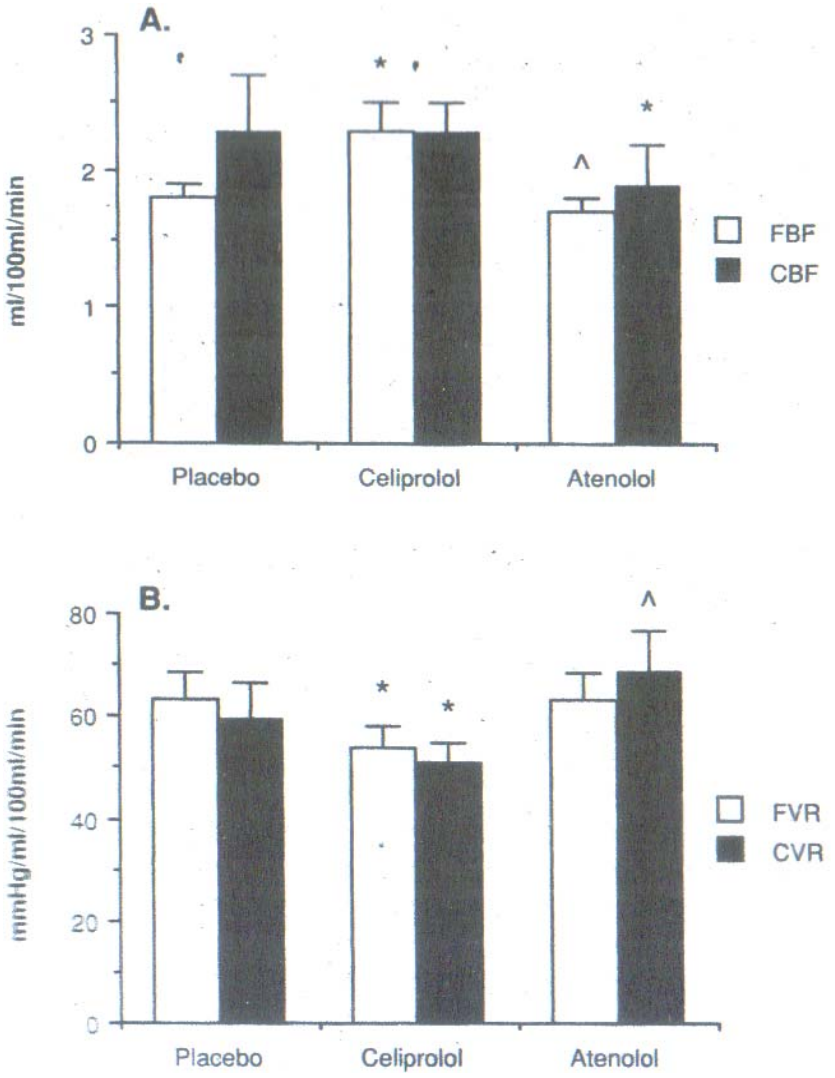


**Figure 1.** (A) Resting forearm (FBF) and calf blood flow (CBF) during the treatment and placebo phases. (B) Resting forearm (FVR) and calf molecular resistance (CVR). *Significant difference from placebo; ^Significant difference between atenolol and celiprolol.

significant. Results are expressed as mean ± standard error (SE).

## RESULTS

### Postceliprolol and postatenolol placebo phases

There were no statistical differences between these two placebo phases for any of the variables to be discussed subsequently. Therefore, for ease of presentation, one mean value from the two phases is used as shown in Figures 1 to 4.

### Peripheral blood flow and vascular resistance

Celiprolol significantly increased resting FBF and decreased CVR compared with both placebo and atenolol and decreased FVR compared with placebo. In contrast, atenolol significantly decreased resting CBF and tended to increase CVR compared to placebo. Compared with celiprolol, CVR was significantly higher and FBF significantly lower with atenolol (Figure 1).

Changes after isolated calf exercise were small and not significant. Treatment with celiprolol produced higher CBF than atenolol (placebo: 9.7; Celiprolol: 9.8; atenolol: 9.4; ml. 100 ml/min) and lower CVR than both placebo and atenolol (placebo: 13.4; celiprolol: 12.8; atenolol: 13.3 resistance units).

### Heart rates and blood pressures during exercise

Not all of the subjects were able to complete the third

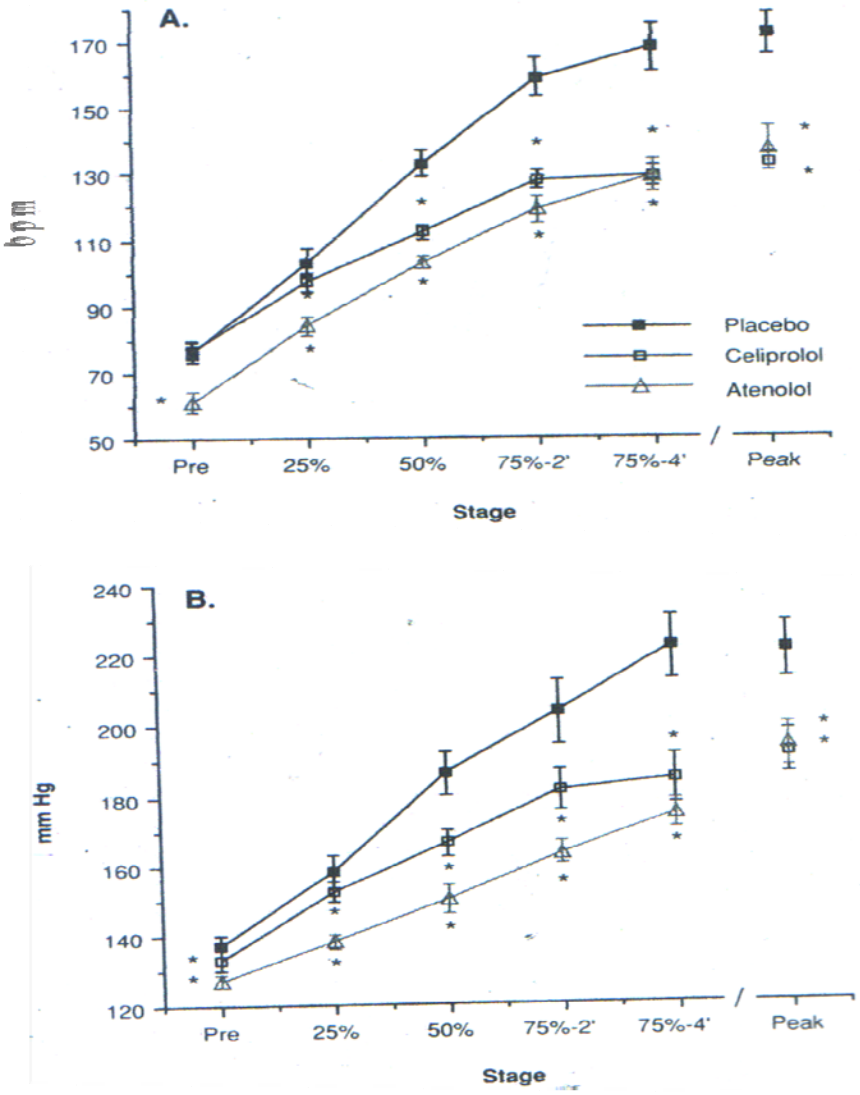


**Figure 2.** (A) Pre-exercise, submaximal (staged protocol) and peak (ramping protocol) heart rates during the treatment and placebo phases. (B) Preexercise, submaximal (staged protocol), and peak (ramping protocol) systolic blood pressures. *Significant difference from placebo.

stage (75%) of the submaximal exercise protocol. Only eight subjects completed 2 min and six subjects completed 4 min of the 75% submaximal stage for all treatment and placebo phases of the study. Data from this stage are thus presented as 75%-2' and 75%-4' and have an N of 8 and 6, respectively preexercise values are those obtained prior to the three stage submaximal exercise protocol and peak values and the higher values obtained during the ramping peak exercise protocol (Figure 2).

Celiprolol had no effect on pre-exercise HR whereas atenolol produced a significant decrease compared with placebo. Both β-blockers significantly blunted submaximal HRs; the effect was more pronounced with atenolol at the 25 and 50% levels, but differences between the two drugs were not present at the 75% level and at peak exercise. Again, only eight subjects were able to complete at least 2 min of the 75% level at every visit and six subjects completed at least 4 min of the 75% stage.

Pre-exercise systolic BPs (SBPs) and diastolic BPs (DBPs) were significantly lower than placebo with both drugs. Submaximal SBPs were significantly decreased especially with atenolol. At 75%-4' and at peak exercise there was no statistical difference between celiprolol and atenolol. Both agents significantly decreased DBP at the 25 and 50% levels with atenolol again being more effective. Differences between the two drugs diminished at the 75% level. Neither significantly decreased 75%-4' or peak DBP, although values while on atenolol tended to be the lowest.

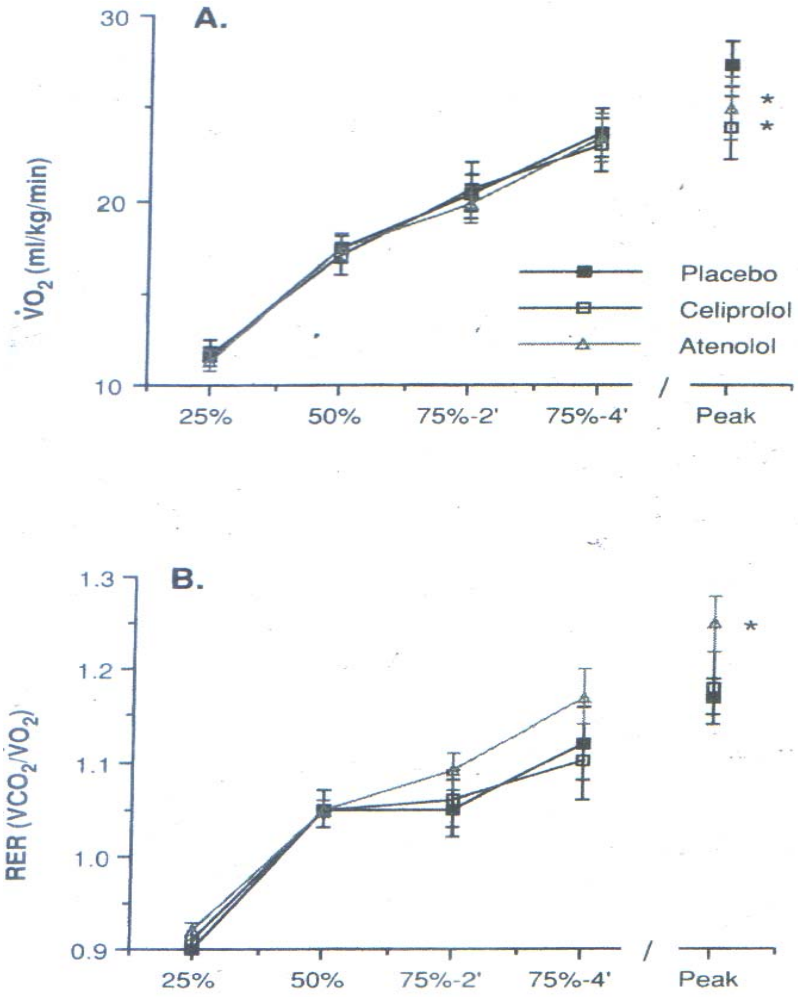


**Figure 3.** (A) Oxygen uptake (ml/kg/min) during submaximal and peak exercise. (B) Respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$) during submaximal and peak exercise. *Significant difference from placebo.

### Ventilatory responses and perceived exertion

Neither β-blocker significantly affected submaximal $\dot{V}O_2$VE nor RER. Both celiprolol and atenolol significantly decreased peak $\dot{V}O_2$ (celiprolol: 23.9±1.7; atenolol: 2 4.9±1.7 ml/kg/min) compared with placebo (27.3± 1.3 ml/kg/min) and did not differ from each other in their effect. There was a significantly elevated respiratory exchange ratio (RER) at peak exercise with atenolol. No significant differences between placebo; celiprolol or atenolol were observed for RPE, during submaximal or peak exercise (Figure 3).

### Total exercise time

Exercise time while on placebo was 13.4 ± 0.7 min and on celiprolol was 12.4 ± 0.6 min and atenolol was 13.2 ± 0.8 min. Only the decrease during the celiprolol phase was significantly different from placebo.

### Decrease in peak $\dot{V}O_2$ and HR

There was a highly significant relationship ($R^2$=0.67; P=0.007; P=0.007) between the percentage decrease in peak HR and the percentage decrease in peak $\dot{V}O_2$ from celiprolol compared with placebo. The same relationship with atenolol did not achieve statistical significance ($R^2$=0.36) (Figure 4).

## DISCUSSION

This study examined peripheral blood flow and exercise responses in untrained middle-aged hypertensive males following chronic administration of celiprolol, atenolol, or placebo. The major findings were: (1) celiprolol, a β-1 adrenoceptor antagonist and β-2 agonist, decreased resting peripheral vascular resistance compared with both placebo and β-1 receptor, antagonist atenolol and tended to produce higher CBF and lower cerebral vascular

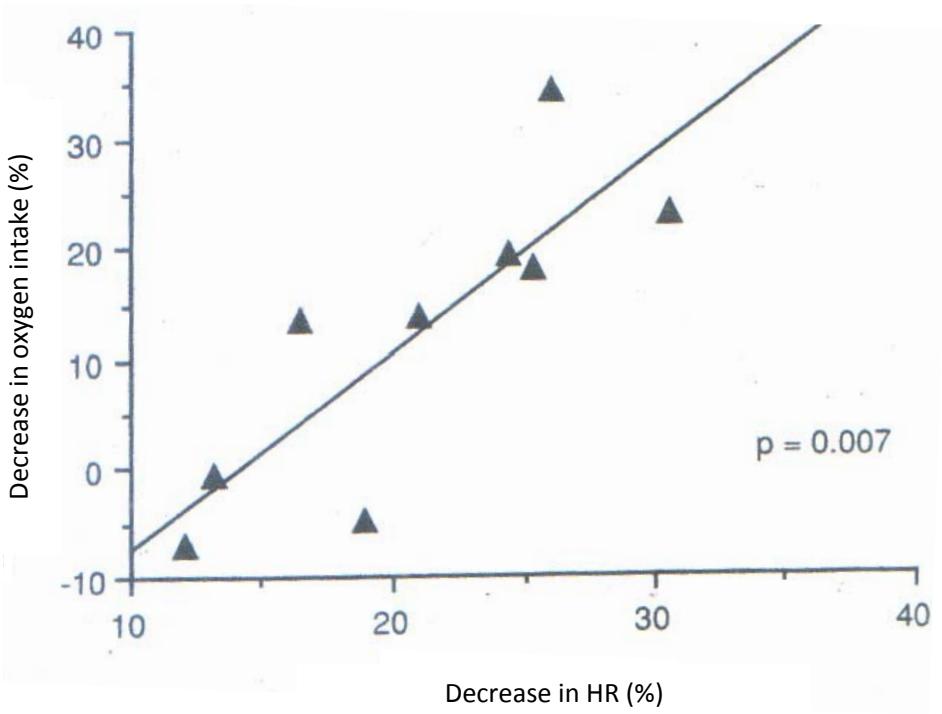


**Figure 4.** Relationship between percentage decrease in peak heart rate (HR) and percentage decrease in peak oxygen uptake during celiprolol treatment. Regression equation: $y = -25.289 + 1.7965x$; $R^2 = 0.67$.

vascular resistance (CVR) after 2 min of isolated calf exercise; (2) neither β-blocker adversely affected submaximal bicycle ergometer exercise in terms of higher RPES or lower $VO_2$; and (3) with a ramping bicycle ergometer protocol, both β-blockers similarly decreased peak $VO_2$ compared with placebo and only celiprolol significantly decreased time to exhaustion.

The increase in resting FBF and decrease in FVR and CVR after 6 weeks of treatment demonstrated celiprolol's β-2 vasodilating properties. Atenolol, on the other hand, significantly increased resting CVR compared with celiprolol. Other investigators also reported a decrease in FVR on celiprolol therapy (Frohlich et al., 1991; Mancia et al., 1986; Trimarco et al., 1987). This study is the first study to do so in the calf of otherwise healthy hypertensive subjects.

A direct measurement of leg blood flow during exercise was not made since this requires invasive procedures. Venous occlusion plethysmography can be used to indirectly assess exercise blood flow if the measurement is made immediately upon cessation of exercise; thus chose to have the subjects perform a bout of reproducible calf exercise, which enabled us to compare their isolated calf exercise CBF and CVR during the treatment and placebo periods. This study was not able to demonstrate significant differences in CBF or CVR after this brief calf exercise, although the tendency was for celiprolol to produce the highest CBF and lowest CVR.

Despite the fact that celiprolol increased blood flow to the extremities at rest and produced less slowing of HR than atenolol, there were no significant differences between the two drugs in terms of fatigue or $VO_2$ during submaximal exercise. In fact, no difference between submaximal variables measured during either drug treatment phase or the placebo phase was observed. These results were somewhat surprising, especially for atenolol, in light of the common complaints of fatigue from patients treated with β-blockers.

However, in a controlled laboratory setting, inconsistent findings for exercise parameters measured during β-blockade have been reported, with some investigators noting no change in oxygen uptake or exercise performance (Petersen et al., 1983; Rogers et al., 1988; Wilmore et al., 1985) and others, a decrease (Kaiser et al., 1986; Thompson et al., 1989). Adverse effects seem to be more consistent following acute β-blockade when reflex vasoconstriction is greatest. There also seems to be more of an increase in subjective fatigue and limitation on exercise performance in younger more active or trained individuals. McLenachan et al. (1991), studying young, trained, normotensive subjects, recorded increased visual analog scores for breathlessness with atenolol and increased scores for muscle fatigue with both celiprolol and atenolol during 8 min of treadmill exercise at 70% of maximal $VO_2$. In this study lack of significant effect during submaximal exercise may be due

to the fact that middle-aged sedentary hypertensive subjects following chronic β-blockade was studied.

In one study similar in design to this, hypertensive subjects treated with 50 to 200 mg atenolol per day for 12 weeks had no significant decrease in $VO_2$ during cycling exercise at 25 and 50 W despite lower HR, unchanged stroke volume, lower cardiac output (Q), and increased total peripheral resistance during exercise. These authors (Prichard and Tomlinson, 1986) as well as others (Lund-Johansen, 1983; Thompson et al., 1989) concluded that in the presence of a limitation in the Q rise during exercise and a limitation of peripheral vasodilator responses to exercise, there is greater reliance on increased oxygen extraction to maintain tissue oxygenation. This would appear to be the case in my subjects who had significantly lower HR with atenolol treatment compared with celiprolol and placebo and yet had similar submaximal values for $VO_2$ during all three treatment regimens.

At peak exercise, increased oxygen extraction was not sufficient to maintain the level of oxygen uptake seen during placebo treatment and both β-blockers significantly decreased peak $VO_2$. There was no longer any difference between celiprolol and atenolol for HR, with both decreasing peak HR by 20%, a finding consistent with other reports (Chick et al., 1988; Head et al., 1997). The direct relationship between the decrease in peak HR and the decrease in peak $VO_2$ was statistically significant only for celiprolol with a coefficient of determination of 0.67. Thus, whereas a decrease in HR and, presumably Q, contributed to the adverse effect of both beta blockers, peripheral factors appeared to play a more important role in limiting peak oxygen uptake with atenolol.

It was also observed a significant increase in peak RER with atenolol. Others have observed an increase in RER with β-blockade and speculated that this may be due to a shift from fat to carbohydrate metabolism since β-blockers can limit the supply of free fatty acids to exercising muscle (Van Baak et al., 1988; Wilmore et al., 1985).

Celiprolol did not offer an advantage over atenolol in terms of peak $VO_2$ and even produced a larger decrease in peak $VO_2$ and even produced a larger decrease in peak exercise time. This suggests that β-2mediated vasodilation may play a secondary role to local metabolic vasodilation (Kowalchuk et al., 1990) or that both vasodilating mechanisms may be limited by α-adrenergic vasoconstriction. The traditional view has been that, during exercise, blood flow is preferentially distributed to active muscles as a result of increased adrenergic tone in inactive vascular beds. A recent theory is that there is generalized sympathetic outflow during exercise that not only shunts blood away from inactive vascular beds but, especially during high-intensity exercise, prevents a fall in blood pressure by partially opposing the extra-ordinary capacity for vasodilation of the exercising tissues (Rowell and O'Leary, 1990). During β-blockade there may be even further limitation of local blood flow by increased α-adrenergic tone secondary to the decreased Q (Pawelczyk et al., 1992). Alternatively, the β-2-celiprolol may interfere with the normal redistribution of Q during exercise by opposing α-adrenergic vasoconstriction in inactive beds and actually "stealing" blood flow away from the exercising muscles.

Thus, celiprolol's vasodilating properties may offer some advantage to hypertensive individuals at rest in terms of better peripheral circulation and less bradycardia but no advantage over conventional β-1 receptor blockade was seen during either submaximal or peak exercise. Further work is needed to determine whether similar conclusions would be reached for females or different age or fitness level individuals.

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