The Effect of Adding β-2 Agonism to improve -1 Blockade Exercise Responses on Hypertensive Patients

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ABSTRACT

This study assesses the Effect of adding -2 Agonism to improve β-1 Blockade Exercise Responses on Hypertensive Patients. The ultimate aim is to test 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. After an initial 3 week 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 ergometry 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 b-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; celoprolol 23.9 ± 1.7, atenolol 24.9 ± 1.7, placebo 27.3 ± 1.3 ml.kg^{-1} min^{-1}. My findings suggest that during exercise while on b-blockade, other factors such as sympathetic vasoconstriction or local metabolic vasodilation may override β-2-mediated vasodilation. Thus the addition of β-2 agonism to β-1 antagonism decreases resting vascular resistance but offers no advantage over conventional β-1 blockade therapy during exercise.

Keywords: *Celoprolol, atenolol, venous occlusion plethysmography, 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 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, 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, broncho-constriction, and generalized fatigue. In addition, maximal exercise capacity is typically reduced by 15-20% on β -blocking agents (Kalser et al, 1986; Lund-Johansen, 1987; Petersen et al, 1983). 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, Smith and Khandwala, 1985). Also, less resting bradycardia has been observed with celiprolol administration, suggesting partial intrinsic sympathomimetic activity (Wheeldon, McDevitt and Lipworth, 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.

METHOD

Research Design: The study is 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 200mg celiprolol QD or 50mg atenolol QD and escalated to 400mg QD and 100 mg QD, respectively, at week 4 if their supine diastolic blood pressure (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 ± 6mmhg, and peak oxygen uptake during the initial placebo washout phase was 26.5 ± 3.6 $ml.kg^{-1}. min^{-1}$. No other medication that would affect blood pressure 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 on over night 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 peak sub maximal bicycle tests. No data from the phase were analysed except for the peak scercise capacity data. The absolute workload

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 11.00am at week 5 for the determination of peak bicycle exercise capacity 5 hours after taking the study pill. At week 6, subjects reported to the lab at 8am. Resting blood pressures in various positions were measured first, resting and sub-maximal blood flow measurements were made at 9am and submaximal bicycle exercise was performed at 11am, again 5 hours 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.

Peripheral blood flow: Forearm (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 pressure pressure). Regional vascular resistance was calculated from MAP/BF, CBF was also measured after 2 minutes of unresisted ankle flexion at the rate of 30^{0} extension and flexion every 2 seconds. 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^{-1}. The test was terminated when the subjects could no longer maintain their chosen pedal speed and the highest *w* 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 minutes during the test. Respiratory variables were measured continuously using a system 2000 metabolic measurement Chart (Medical Graphics Corporation).

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

Data Analysis: Conventional descriptive statistics were used for subject characteristics; values are presented as mean ± SD, stepwise student's paired t-tests were used to detect differences in means during treatment phases: 1) two tailed t-tests were used to detect differences between the two placebo phases: post celiprolol placebo phase (that following the celiprolol treatment phase) and post atenolol placebo phase (that following the atenolol treatment phase, 2) one tailed t-tests were used to detect a significant effect from celiprolol compared with the post celiprolol placebo phase and a significant effect from atenolol compared to the post atenolol placebo phase; the Bonteroni. 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 significant. Results are expressed as mean ± SE.

RESULTS AND DISCUSSION

Post celiprolol and Post atenolol Placebo Phases: There were no statistical differences between these two placebo phases for any of the variables to be discussed below. Therefore, for ease of presentation, one mean value from the two phases is used in the figures that follow.

Peripheral Blood Flow and Vascular Resistance **(Fig. 1a):** 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. Changes after isolated calf exercise were small and not significant. Treatment with celiprolol tended to produce higher CBF than atenolol (placebo: 9.7; Celiprolol: 9.8; atenolol: 9.4; ml. 100 ml^{-1} min^{-1}) and lower CVR than both placebo and atenolol (placebo: 13.4; celiprolol: 12.8; atenolol: 13.3 resistance units).

Exercise Heart Rates and Blood Pressures **(Fig. 1b):** Not all of the subjects were able to complete the third stage (75%) of the submaximal exercise protocol. Only eight subjects completed 2 minutes and six subjects completed 4 minutes 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 pre exercise 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. Celiprolol had no effect on pre exercise HR whereas atenolol produced a significant decrease compared with placebo. Both â-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 minutes of the 75% level at every visit and six subjects completed at least 4 minutes 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 scercise 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.

Ventilatory responses and perceived exertion **(Fig. 2a):** Neither B-blocker significantly affected submaximal VO_2 VE, nor RER. Both celiprolol and atenolol significantly decreased peak VO_2 (celiprolol: 23.9 ± 1.7; atenolol: 2 4.9 ± 1.7 ml. kg^{-1}. min^{-1}) compared with placebo (27.3 ± 1.3ml. $kg^{-1}min^{-1}$) and did not differ from each other in their effect there was a significantly elevated RER at peak scercise with atenolol no significant differences between placebo; celiprolol, or atenolol were observed for RPE, during submaximal or peak exercise.

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

Decrease in peak VO_2 and HR **(Fig. 2b):** 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 VO_2 from celiprolol compared with placebo. The same relationship with atenolol did not achieve statistical significance (R^2 = 0.36). This study examines peripheral blood flow and exercise responses in untrained middle-aged hypertensive males following chronic administration of celiprolol, atenolol, or placebo. The findings show that celiprolol, a β -1 adenoceptor antagonist and β -2 agonist, decreased resting peripheral vascular resistance compared with both placebo and the β -1 receptor, antagonist atenolol and tended to produce higher CBF and lower CVR after 2-minutes of isolated calf exercise.

Neither β -blocker adversely affected submaximal bicycle ergometer exercise in terms of higher RPES or lower VO_2. With a ramping bicycle ergometer protocol, both â-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 celoprolol'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, Grassi and Parati, 1986; Trimarco, Lembo and Deluka 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, the subjects were allowed to perform a bout of reproducible calf exercise, which enabled the researcher to compare their isolated calf exercise CBF and CVR during the treatment and placebo periods. The study was not able to demonstrate significant differences in CBF or CVR after this brief calf exercise, although the tendency was for celoprolol to produce the highest CBF and lowest CVR. Despite the fact that celoprolol 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, there is no difference between submaximal variables measured during either drug treatment phase and the placebo phase. These results were some what 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, Freund and Joyner, 1985) and others, a decrease (Kalser 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, mormotensive subjects, recorded increased visual analog scores for breathlessness with atenolol and increased scores for muscle fatigue with both celiprolol and atenolol during 8 minutes 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 the subject were middle-aged sedentary hypertensive subjects following chronic β -blockade.

In one study similar in design to this, hypertensive subjects treated with 50-200 mg atenolol per day for 12 weeks had no significant decrease in VO_2 during cycling exercise at 25 and 50W despite lower HR, unchanged stroke volume, lower cardiac output (*Q*), and increased total peripheral resistance during exercise. Prichard and Tomlinson (1986); Lund-Johansen (1983); Thompson et al (1989) conclude 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 the subjects used in the study 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 â-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). 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. Also, a significant increase in peak RER with atenolol was observed. 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, Koene and Verstappen, 1988; Wilmore Freund, and Joyner, 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 -2-mediated vasodilation may play a secondary role to local metabolic vasodilation (Kowalchuk, Klein, and Hughson 1990) or that both vasodilating mechanisms may be limited by β -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 β -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 β -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.

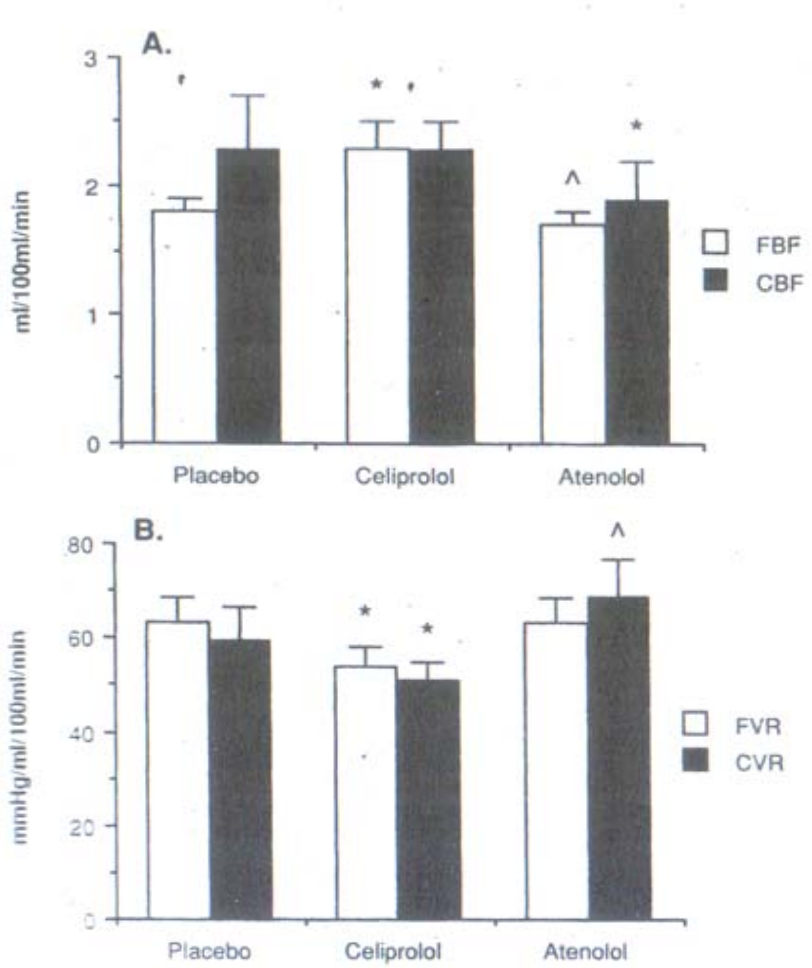

Figure 1 A: Resting forearm (FBF) and calf blood flow (CBF) during the treatment and placebo phases. **Figure 1B:** Resting forearm (FVR) and calf molecular resistance (CVR). *significant difference from placebo; ^ = significant difference between atenolol and celiprolol.

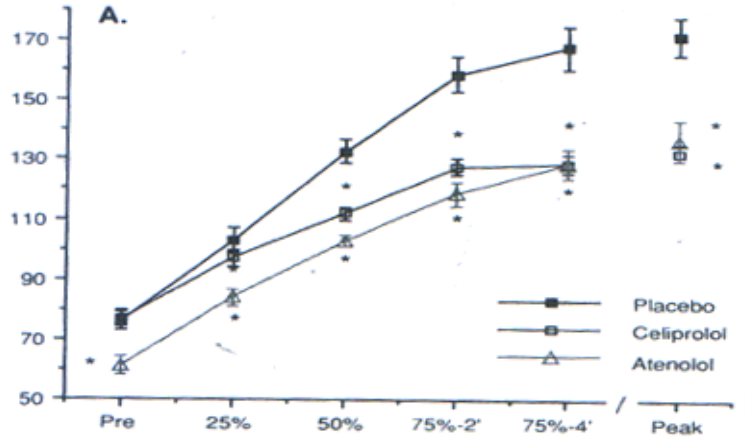

Figure 2A: Preexercise, submaximal (staged protocol), and peak (ramping protocol) heart rates during the treatment and placebo phases.

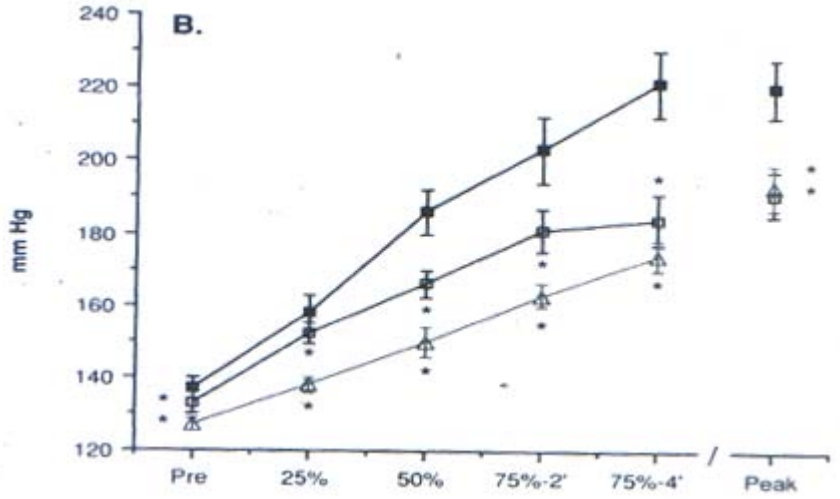

Figure 2B: Preexercise, submaximal (staged protocol), and peak (ramping protocol) systolic blood pressures. * significant difference from placebo

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