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Atorvastatin Increases Exercise Leg Blood Flow in Healthy Adults

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Abstract

OBJECTIVES—We sought to examine the effect of atorvastatin therapy on exercise leg blood flow in healthy middle-aged and older, men and women.

BACKGROUND—The vasodilatory response to exercise decreases in humans with aging and disease and this reduction may contribute to reduced exercise capacity.

METHODS—We used a double-blind, randomly assigned, placebo-controlled protocol to assess the effect of atorvastatin treatment on exercising leg hemodynamics. We measured femoral artery blood flow (FBF) using Doppler ultrasound and calculated femoral vascular conductance (FVC) from brachial mean arterial pressure (MAP) before and during single knee-extensor exercise in healthy adults (ages 40–71) before (PRE) and after (POST) 6 months of 80 mg atorvastatin (A: 14 men, 16 women) or placebo (P: 14 men, 22 women) treatment. FBF and FVC were normalized to exercise power output and estimated quadriceps muscle mass.

RESULTS—Atorvastatin reduced LDL cholesterol by approximately 50%, but not in the placebo group ($p < 0.01$). Atorvastatin also increased exercise FBF from 44.2 ± 19.0 to 51.4 ± 22.0 mL/min/W/kg muscle whereas FBF in the placebo group was unchanged (40.1 ± 16.0 vs 39.5 ± 16.1) ($p < 0.01$). FVC also increased with atorvastatin from 0.5 ± 0.2 to 0.6 ± 0.2 mL/min/mmHg/W/kg muscle, but not in the placebo subjects (P: 0.4 ± 0.2 vs 0.4 ± 0.2) ($p < 0.01$).

CONCLUSIONS—High-dose atorvastatin augments exercising leg hyperemia. Statins may mitigate reductions in the exercise vasodilatory response in humans that are associated with aging and disease.

Keywords

Atorvastatin; leg vasodilation; exercise hyperemia

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INTRODUCTION

The leg vasodilatory response to exercise (leg exercise hyperemia) is reduced in older sedentary (1) and trained (2) men and women (3) as well as in patients with Type 2 diabetes (4), chronic heart failure (5) and peripheral arterial disease (6). Reductions in blood flow may contribute to reduced exercise capacity in these patients (7) and/or increased systemic vascular resistance during large muscle dynamic exercise (8).

Hydroxy-methylglutaryl (HMG) CoA reductase inhibitors (statins) have wide-reaching effects on human vascular function beyond their direct benefits in reducing LDL-C. These vascular effects include reductions in circulating endothelin-1(9), sympathetic outflow (10) and reactive oxygen species (11) as well as increases in the production of nitric oxide synthase and improvements in endothelial function (11). Statins are also direct vasodilators (12). Collectively these statin vascular effects suggest that statins could mitigate age- and disease-related reductions in leg exercise hyperemia.

The present investigation determined the effect of 6 months of atorvastatin 80mg treatment on the leg hyperemic response to exercise in healthy middle-aged and older men and women. We hypothesized that statin treatment would increase FBF and FVC during exercise.

METHODS

Subjects

Subjects in the present study were selected from the larger STOMP trial ((The Effect of **ST**atins **On** Muscle **P**erformance, National Heart, Lung and Blood Institute 5R01HL081893-04, NCT00609063), a double-blind, random-assignment clinical trial investigating the effects of statins on muscle performance in healthy, normally active adults. All STOMP subjects > age 40 at the Hartford Hospital study site were enrolled in this sub-study unless they refused testing or their femoral artery could not be adequately imaged. Four subjects that began the sub-study dropped out of the parent study and subsequently were not included in analyses since no post-study measurements were obtained. STOMP subjects were normotensive (resting blood pressure $\leq 140/90$ mmHg on or off anti-hypertensive treatment) and free of overt chronic diseases as evaluated by medical questionnaire, physical examination, resting electrocardiogram, and maximal treadmill exercise testing. Subjects had not previously been treated with a statin and were not using any non-statin cholesterol-lowering medications. Women who were amenorrheic in the preceding 12 months were considered postmenopausal, those amenorrheic in the preceding 3–12 months were considered perimenopausal (none in the current study), and all other women were classified as premenopausal (13). Subjects provided written, informed consent as approved by the Institutional Review Board at Hartford Hospital and consistent with the Declaration of Helsinki guidelines.

Study Protocol

STOMP subjects completed three study visits prior to randomization to statin (atorvastatin 80mg; Pfizer, Inc., New York, NY) or placebo and two visits after 6 months of treatment, as described and diagramed previously (14). Fasting blood lipid levels, physical activity assessment, anthropometric measurements, treadmill exercise testing with expired gas measurement, and muscle strength testing of the dominant arm and leg were performed as described.

For the current substudy, subjects' physical activity levels were represented by Question #6 of the Paffenbarger Physical Activity Questionnaire (PPAQ) (15). In Question 6, subjects

were asked how many times a week they participated in “regular activity akin to brisk walking, jogging, bicycling, swimming, etc. long enough to work up a sweat, get [their] heart thumping, or get out of breath.”

Exercising leg blood flow measurements were performed on the subset of STOMP study subjects participating in this substudy. Specifically, on the 3rd pre-study and 2nd post-study visits, subjects performed one, 5 minute bout of single-knee extension exercise at a cadence of 40 kicks/minute using the Biodex System 3 as previously described (16). Single knee extensor exercise is not limited by cardiac output and elicits less excitation of the sympathetic nervous system than two-legged exercise, and is thus effective for examining the leg vasodilatory response to exercise independent of central limitations and alterations (3). Briefly, subjects were instructed to contract the quadriceps muscle on extension of the lever arm of the Biodex to generate 20–30 N·M of force (corrected for each subject’s resting limb weight) through a 90–180° range of motion, which corresponded to an approximate 10W workload. Subjects were also instructed to relax on return of the lever arm to minimize engagement of hamstrings.

Data Acquisition and Measurements—Blood pressure was measured in the last minute of rest and the last minute of kicking exercise using manual auscultation in the right arm. A Doppler ultrasound machine (Terason t3000, Burlington, MA) equipped with a high resolution 7–12 MHz linear-array transducer was used to measure mean blood velocity and vessel diameter of the left common femoral artery. Velocity measurements were taken during the last minute of rest and the last minute of kicking exercise. A high-resolution diameter measurement was taken in 2D mode to optimize imaging at rest and used to calculate resting and exercising blood flow. The use of resting diameter is possible because our previous work shows that femoral diameter does not change significantly ($\leq 1\%$ dilation) in men or women when exposed to the shear rates evoked by this moderate workrate (3). Velocities were processed using the Terason’s analysis software to calculate mean blood velocities. Diameter images were analyzed using edge-detection software (Brachial Analyzer Software, Medical Imaging Applications; Iowa City, IA). Diameter measurements were always calculated from the intima-lumen interface at both the distal and proximal vessel wall and approximately 100 frames were averaged across the cardiac cycle.

Data Analysis and Computations—Mean arterial pressure (MAP, in mmHg) was calculated as $(1/3 \text{ systolic pressure}) + (2/3 \text{ diastolic pressure})$. FBF was calculated by multiplying the cross-sectional area of the femoral (the diameter taken at rest) with mean blood velocity (V_{mean} ; cm/s). FVC was calculated as FBF/MAP . Both FBF and FVC were normalized to the power generated during the entire kick cycle. We have previously established the within-subject coefficient of variation for exercising leg blood flow (normalized to power output) in this model as $4.9 \pm 1.6\%$ (16). Thigh volume was estimated anthropometrically from thigh patellar-pubic length, skinfold thicknesses, and circumference (17). Quadriceps femoris muscle mass was then estimated from thigh volume (18) and FBF and FVC were normalized to estimated quadriceps muscle.

Statistical Analyses

Between group differences at baseline were assessed using a two-way ANOVA to examine the effects of sex, drug, and the sex*drug interaction. A repeated measures ANOVA (alone and adjusted for statistically significant covariates) with drug, sex, and the drug*sex interaction as the between-subject factors and time as a within-subjects factor was used to assess the effect of atorvastatin on baseline characteristics, blood lipids and leg hemodynamics. Post-hoc comparisons with the Tukey-Kramer correction were performed if main or interaction effects were significant. Pearson correlations were used to determine

relations between changes in leg hemodynamic parameters and LDL-C and/or leg hemodynamic responses at baseline. Statistical significance was accepted at $p < 0.05$. Statistical analyses were performed with SAS 9.1.2 (Cary, NC) and all data are expressed as group means $\pm$ standard deviation (SD).

RESULTS

Subject Characteristics

Women at baseline had lower muscle mass and strength and exercise capacity than men, but there were minimal baseline differences between men or women assigned to the drug or placebo groups (Table 1). Four women and no men reported regular cigarette smoking; 3 placebo men and 2 women (1 on placebo; 1 on atorvastatin) reported use of antihypertensive medications; 24 women were postmenopausal (10 on atorvastatin and 14 on placebo); and 4 women reported use of hormone therapy (3 on atorvastatin and 1 on placebo).

Changes in Baseline Characteristics During the Study

Maximal oxygen uptake decreased regardless of drug or sex during the study (VO_{2max} : 29.4 ± 7.4 to 28.6 ± 7.1 mL/kg/min in all subjects combined, ($p < 0.01$)). There were no other significant effects of time on any Table 1 baseline variable (all $p > 0.08$), nor were there any time*drug interactions (all $p > 0.31$), time*sex interactions (all $p > 0.17$), or time*drug*sex interactions (all $p > 0.09$) observed in these variables pre-post study. In addition, there was no effect of time, drug or the time*drug interaction (all $p > 0.17$) on the power generated during knee extensor exercise (Pre-study vs. post-study work rate: 10.9 ± 2.5 vs. 10.5 ± 2.5 W), although the power generated during knee flexion decreased slightly across the study ($p < 0.01$) in both groups ($p = 0.27$ for interaction; Pre-study vs. post-study work rate: 2.8 ± 2.7 vs. 2.0 ± 1.6 W).

Effect of 6 months of Atorvastatin Therapy on Blood Lipids

Atorvastatin reduced LDL-C in men and women equally ($p = 0.51$ for time*drug*sex interaction) by approximately 50% (-1.8 ± 0.9 mmol/L) whereas the placebo group was unchanged ($+0.1 \pm 0.4$ mg/dL) ($p < 0.01$). Atorvastatin also reduced HDL-C (-0.1 ± 0.2 mmol/L) and triglycerides (-0.3 ± 0.6 mg/dL) whereas the placebo group was again unchanged ($+0.03 \pm 0.2$ and -0.01 ± 0.4 mg/dL) ($p < 0.05$ for both).

Effect Atorvastatin on Resting Leg Hemodynamics

Repeated measures analyses revealed no significant time*drug*sex and time*sex interaction (all $p > 0.17$) for resting leg hemodynamics. Consequently, resting FBF (Figure 1A), resting FBF normalized to estimated quadriceps muscle (Figure 1B), resting FVC (Figure 1C) and resting FVC normalized to estimated quadriceps muscle (Figure 1D) are presented as group means with men and women combined. While resting FBF, normalized resting FBF and normalized resting FVC pre- and post-study were lower in the placebo group than statin group ($p = 0.03$, 0.01 and 0.03 , respectively) and women exhibited higher normalized resting FBF and FVC than men (both $p = 0.02$), there was no effect of atorvastatin treatment on any of these parameters (all $p > 0.54$).

Effect of Atorvastatin on Exercising Leg Hemodynamics

Repeated measures analyses revealed no significant time*drug*sex and time*sex interactions (all $p > 0.37$) for exercising leg responses. Consequently, exercising FBF (Figure 2A), exercising FBF normalized to estimated quadriceps muscle (Figure 2B), exercising FVC (Figure 2C) and exercising FVC normalized to estimated quadriceps muscle (Figure 2D) are presented as group means for men and women combined. In contrast to

resting hemodynamics, the time*drug interaction was significant for all four parameters (all $p < 0.02$), as atorvastatin significantly augmented leg exercise hyperemia compared to placebo. Adjusting for significant ($p < 0.05$) covariates including age, VO_{2max} , change in systolic blood pressure pre-post study (all 4 models), and change in body mass index pre-post study (non-normalized FBF and FVC models only) did not alter the effect of atorvastatin on outcomes, and there were no significant interactions of these covariates with the time*drug effect (all $p > 0.20$). Univariate correlations between pre- and post-study FBF and FVC and these covariates are shown in Table 2.

Similar to resting parameters, women exhibited higher muscle mass-normalized exercising FBF and FVC pre- and post- study than men (both $p < 0.01$). Consequently, women were also assessed alone in the model and classified according to menopausal status (pre- or post-menopausal). Although there was a significant effect of menopause on FBF, FVC, and normalized FVC such that premenopausal women exhibited greater exercise hyperemia than postmenopausal women throughout the study (all $p < 0.05$), there was no significant drug*menopause interaction observed with the effect of atorvastatin on exercising leg hemodynamics (all $p > 0.31$).

DISCUSSION

This study is, to our knowledge, the first study to investigate the effect of statin therapy on limb exercise hyperemia. High-dose atorvastatin treatment had no effect on resting leg hemodynamics, but significantly improved FBF and FVC during single knee extensor exercise in both men and women.

Substantial evidence has established a benefit of statin therapy on non-exercise hyperemic responses in the forearm vasculature (19;20). The present study documents that statin therapy increases leg exercise hyperemia. The leg is a hemodynamically significant vascular bed for systemic cardiovascular control, locomotion and large muscle mass dynamic exercise capacity (21). Therefore, the observation that high dose atorvastatin increases both exercising FBF and FVC during single knee extensor exercise suggests that statin therapy may be an effective strategy to mitigate age- and disease-related declines in exercising leg blood flow, thus potentially improving exercise tolerance and/or blood pressure regulation in aging and clinical populations.

Emerging evidence supports sex-specific modulation of the cardiovascular system. Therefore, we examined whether there were sex differences in the effect of atorvastatin on exercising leg hemodynamics. Interestingly, atorvastatin improved FBF and FVC equally in men and women. Post-menopausal status has been associated with lower forearm reactive hyperemia and basal leg blood flow (22;23), but menopausal status did not influence the improvement in exercise hyperemia with atorvastatin in the present study.

There were, however, several additional covariates that significantly affected exercising leg hemodynamics, suggesting that leg vasodilation is affected by multiple cardiovascular risk factors. Greater age and increases in systolic blood pressure pre- to post-study were inversely associated with leg exercise hyperemia, and increases in body mass index during the study were directly associated with leg exercise hyperemia. The latter was most likely due to volumetric scaling since the association disappeared with normalization to muscle mass. Surprisingly, baseline fitness (i.e., VO_{2max}) was also inversely associated with leg exercise vasodilatory response. Previous work has shown that older endurance-trained men exhibit reduced leg blood flow during dynamic exercise relative to young men (2). Thus the inverse association with cardiorespiratory fitness in this middle-aged and older population may represent improved oxygen extraction and/or efficiency, reducing the blood flow

required for leg exercise. Nonetheless, controlling for age, VO_{2max} , and changes in blood pressure/body mass in the repeated measures model did not reduce the effect of atorvastatin on exercising FBF and FVC.

Atorvastatin could affect leg exercise hyperemia by altering local and/or systemic regulation of muscle blood flow via multiple mechanisms. Local mechanisms include an increase in nitric oxide bioavailability and extracellular adenosine formation (24) as well as a decrease in arginase activity (20). Statins also systemically reduce inflammation, sympathetic nervous system activity and oxidative stress (10;25). Notably, the mechanism underlying augmented leg exercise hyperemia appears to be independent of the cholesterol-lowering effects of atorvastatin since there was no correlation between reductions in LDL-C and increased FBF or FVC (all $p > 0.48$). Increased forearm vasodilation with statin therapy has also occurred independent of changes in LDL-C, (19) further suggesting that the vascular benefits of statins are attributable to a non-lipid-lowering (pleiotropic) mechanism. There was also no effect of 80 mg atorvastatin on basal leg blood flow or vascular conductance in the current study, suggesting that statins augment exercise hyperemia by a mechanism unique to, or augmented by, the heightened metabolic demand of an exercise stimulus.

The current investigation was a placebo-controlled, double-blind study design, but there remain limitations to the study. Participants were not selected to have an attenuated leg exercise hyperemic response at baseline so we cannot be certain that similar increases in leg blood flow and conductance occur with subjects with abnormal baseline values, although there was no significant correlation between baseline exercising leg blood flow or vascular conductance and changes in these parameters with statin therapy so it is less likely that the response would differ in subjects with impaired baseline values. Also, statin therapy in patients with claudication improves walk time to pain (26) suggesting that improvements in blood flow do occur in patients with documented disease. Also, we studied only 80 mg atorvastatin so we cannot determine if our observation of increased exercise blood flow and conductance applies to other statins and/or doses. We assumed that femoral artery diameter did not change with exercise. This is consistent with our prior data (3;27) but was not re-examined in the present study. We provided oral and visual feedback to our subjects to minimize force production during knee flexion. Nevertheless, subjects still generated ~2–3 W force during the flexion phase of the exercise. We normalized hemodynamic responses to the force produced during extension *and flexion* to account for any inter-individual differences in metabolic demand associated with the exercise modality, but recognize that some subjects might have increased their muscle metabolic demand by exerting more flexion force.

CONCLUSIONS

Despite these limitations, this study is to our knowledge the first to demonstrate improvements in exercise hemodynamics with statins and has several clinical implications. First, it suggests that some of the improvement in exercise tolerance demonstrated in claudication patients with statin therapy (26) may be due to a direct effect on arterial conductance. Second, statins are known to produce myalgia that is clinically more apparent in physically active subjects, and is provoked by exercise (28). Also, statins exacerbate the increase in creatine kinase produced by exertion (29). Our present results suggest that this effect is not due to reduced exercise blood flow (30). Finally, our results suggest that the improvement in exercise hemodynamics are independent of LDL reduction adding improved exercise leg hemodynamics to the potential pleiotropic effects of statins. Notably, the ~20–25% increase in leg exercise hyperemia observed in the current study is equivalent to the magnitude of impairment observed in older adults or patients with Type II diabetes and heart

failure (4;5;16). Therefore, statins may also be an effective therapy for treating blunted exercise hyperemia.

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Figure 1.

Effect of atorvastatin on resting leg hemodynamics. Group means $\pm$ SDs for resting FBF (Figure 1A), resting FBF normalized to estimated quadriceps muscle (Figure 1B), resting FVC (Figure 1C) and resting FVC normalized to estimated quadriceps muscle (Figure 1D). * indicates a significant ($p < 0.05$) pre-treatment difference between the placebo vs. atorvastatin group.

Figure 2.

Effect of atorvastatin on exercising leg hemodynamics. Group means $\pm$ SDs for exercising FBF (Figure 2A), exercising FBF normalized to estimated quadriceps muscle (Figure 2B), exercising FVC (Figure 2C) and exercising FVC normalized to estimated quadriceps muscle (Figure 2D). Significant ($p < 0.05$) time*drug interactions are denoted on each panel, and † indicates a significant post-treatment difference between the placebo and atorvastatin group.

Table 1

Baseline Characteristics

	Men		Women		Effect
	StatIn	Placebo	StatIn	Placebo	
N	14	14	16	22	
Age (years)	55 ± 8	57 ± 7	49 ± 12	53 ± 12	
BMI (kg/m ²)	26.1 ± 4.0	26.1 ± 3.4	25.9 ± 4.7	24.6 ± 3.3	
Waist Circumference (cm)	92.4 ± 7.5	95.1 ± 7.8	79.1 ± 12.6 [*]	82.0 ± 8.6 [*]	S
VO _{2max} (mL/kg/min)	35.7 ± 5.3	33.9 ± 7.3	26.6 ± 4.5 [*]	24.7 ± 5.9 [*]	S
PPAQ Q6 (times/wk)	2.8 ± 2.1	3.6 ± 2.3	1.9 ± 1.7	2.0 ± 2.5 [*]	S
Resting SBP (mmHg)	116 ± 6	113 ± 9	111 ± 10	111 ± 14	
Resting DBP (mmHg)	70 ± 7	73 ± 5	74 ± 10	68 ± 9	I
Quad Muscle (kg)	2.5 ± 0.4	2.5 ± 0.4	1.8 ± 0.2 [*]	1.8 ± 0.2 [*]	S
Isometric Strength (N-M)	195 ± 47	188 ± 45	128 ± 32 [*]	131 ± 31 [*]	S
LDL Cholesterol (mmol/L)	3.4 ± 0.6	3.1 ± 0.7	3.4 ± 1.2	3.1 ± 0.7	
HDL Cholesterol (mmol/L)	1.4 ± 0.4	1.5 ± 0.4	1.8 ± 0.4 [*]	1.8 ± 0.4	S
Triglycerides (mmol/L)	1.6 ± 1.0	1.1 ± 0.4 [†]	1.1 ± 0.5 [*]	1.0 ± 0.4	D, S

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; VO_{2max} = maximal oxygen uptake; PPAQ Q6 = times/week subjects reported participating in regular physical activity; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein. Effect denotes a significant (p < 0.05) effect of drug treatment (D), sex (S), or the drug-by-sex interaction (I) observed with a two-way ANOVA;

^{*} indicates a significant difference between men and women within a treatment group; and

[†] indicates a significant difference between treatment groups within the same sex.

Table 2

Pearson correlation coefficients for significant covariates and leg exercise parameters

	VO _{2max}	Age	Δ BMI	Δ SBP
Pre FBF	-.16	-.16	.25*	-.33**
Pre normalized FBF	-.41**	-.11	.21	-.31*
Pre FVC	-.10	-.23	.28*	-.34**
Pre normalized FVC	-.34**	-.18	.25*	-.32*
Post FBF	-.14	-.26*	.04	-.19
Post normalized FBF	-.33**	-.19	.00	-.16
Post FVC	-.05	-.35**	.04	-.28*
Post normalized FVC	-.24	-.28*	.00	-.24

ΔBMI = Change in body mass index post-pre treatment; ΔSBP = change in resting systolic blood pressure post-pre treatment; FBF = exercising femoral blood flow; FVC = exercising femoral vascular conductance; normalized = normalized to estimated quadriceps muscle mass; pre = baseline value; post = post-treatment value.

* Correlation is significant at $p < 0.05$;

** Correlation is significant at $p < 0.01$.