Title Page

Simvastatin Improves Arterial Compliance in High Risk Patients

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Support: Grant from Merck Co., Inc

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Abstract

Background: Reduced arterial compliance is associated with arteriosclerosis. In some arteries, this is due in part to muscle tone, which can be altered by LDL cholesterol reduction and statin therapy. We tested the effectiveness of statin therapy in improving arterial compliance in patients with manifest coronary disease (CAD) and/or diabetes.

Methods and Results: Simvastatin (40 mg/day) was administered to 10 patients with proven CAD for four months. As measured by air plethmysmography, compliance of the arterial segments in the thigh improved in every patient after two months, increasing by 34% by the fourth month. Compliance at the calf was not effected. These results suggest that compliance in the thigh is controlled by smooth muscle tone.

Conclusion: Compliance measurements in the thigh and calf may be a useful measurement in evaluating high-risk patients and monitoring cholesterol lowering therapy.

Introduction

A reduction in arterial compliance is a manifestation of arteriosclerosis and a risk factor for related clinical events (1,2). Compliance is determined by the amount and organization of collagen and elastin and also by the smooth muscular tone in the muscular arteries. Prior studies have found increases in compliance of some arteries after long-term statin treatment (1 year) (3,4,5). In one short-term study (1 month) changes were observed in the leg arteries but not aorta or iliac vessels (6). These effects are apparent in as little as a few days to a month (7,8). Using a device that measures the volume change of arteries in regions of the lower extremities (9,10), we have assessed the effects of simvastatin treatment on arterial compliance in patients with coronary disease or coronary artery disease equivalence according to NCEP guidelines (11).

Methods

A total of ten (10) patients were included in the study, eight men and two women with a mean age of 54 years (range: 42 - 73). The men had a myocardial infarction, revascularization procedure, or arteriosclerotic lesions on imaging studies. The women and four of the men had diabetes mellitus. Patients were excluded, for any of the following: inflammatory disease or active infection, obstructive peripheral vascular disease, use of drugs that change lipoprotein levels, lipid lowering therapy present during the previous 4 weeks or if a clinical event or revascularization procedure had occurred within 6 months. All had been without statin therapy for more than four weeks. Baseline assessment included physical examination, routine laboratory tests (Atlanta VAMC clinical laboratories), lipoprotein analysis (Emory Lipid Research Laboratory), and arterial compliance in the calf and thigh. The latter procedure was done by air plethysmography using the VASOGRAM device as instructed in the instrument manual (VASOCOR, Inc, Charleston, SC). Simvastatin, 40mg daily, was begun and the patients were seen monthly for measurement of blood lipids and arterial compliance. The study was approved by the Institutional Review Board of Emory University and the Research and Development Committee of the Atlanta VAMC.

The air plethysmograph used in these studies is equipped with an internal calibration device to automatically convert pressure changes to volume changes during the measurement (9,10). The computer-controlled machine automatically monitors blood pressure in the arm using a standard cuff. Specially designed pressure cuffs are placed on the thigh and calf for the compliance measurement. The cuff on the calf is inflated to 50 mm HG pressure, then increased in10 mm increments and the pulse volume wave is measured sequentially until the maximum pulse volume is recorded, theoretically at diastolic pressure in the leg. A precise volume (0.6ml) of air is rapidly withdrawn from the cuff during each series of measurements and the computer recalculates the pressure volume relationship (?P/?V) at that cuff pressure. Compliance is then calculated as the pulse volume change under the cuff divided by the pulse pressure normalized to a pulse pressure of 50 mm Hg (MaxV50). The procedure requires approximately 15 minutes. In a multicenter study, without intervention, the MaxV50 measure recorded on three separate clinic visits had a variation of 9% to 10% in the same subject (Unpublished Observations). Normal values for over 300 healthy subjects at the calf are 1.7 (0.6 (Mean (SD) ml for females and 2.5 (0.7 ml for males and at the thigh, are 3.6 (.9 ml for females and 4.9 (1.1 ml for males (13).

Statistical methods

The MaxV50 at the thigh and calf at each month of follow up was compared to baseline values by the paired, two-tailed Student's t-test.

Results

At baseline, the group mean (+ SD) were: total cholesterol - 206 (58 mg/dl, LDL cholesterol (LDL-C) - 135 (50 mg/dl, HDL cholesterol (HDL-C) - 39 (11 mg/dl, and triglycerides -177 (120 mg/dl. The LDL-C decreased to 88 (30 mg/dl ($p<0.001$) at one month and to 89 (46 mg/dl ($p<0.001$) after four months of simvastatin. The HDL-C did not change significantly during the treatment period. The triglycerides decreased to 146 mg/dl at one month and 147 (112 mg/dl at 4 months, both of which were non-significant changes.

The mean calf MaxV50 was 1.82 ml at the calf and 2.99 ml at the thigh before simvastatin was started. The MaxV50 in the thigh increased to 3.71 ml at one month ($p<0.05$), 3.99 at two months ($p<0.001$) and 4.03 ml (34%) at 4 months ($p=0.06$). (See figures 1 and 2). Compliance at the calf was not significantly changed at any visit.

This study did not use placebo controls because most of the subjects had active coronary disease, a well-documented clinical indication for statin therapy. It was felt unethical to deny this treatment for patients for a period of five months. To document stability of the measurement in comparable patients, a group of 41 subjects with more than 20% Framingham 10 year risk (32) or known coronary disease (9) were identified. . Half of these subjects (20) had been taking statin therapy for months and remained on statins. The other half (21) was not on statin therapy for various reasons and remained off statin therapy. Figure 3 shows the results of measures of thigh compliance on separate days over a four-week period in these subjects. Thigh compliance was stable over the follow up period.

Discussion

This study shows a 20% increase in compliance of arteries in the thigh after 1 month of treatment with simvastatin and a 33% increase after two months($p<0.001$)with maintenance through the remaining two months. The rapid response strongly suggests that the effect of this statin is on the muscular tone. In a previous study, flow-mediated dilatation of the brachial artery improved after only one month of treatment with simvastatin and improved further after two months (7). Cerivastatin treatment was found to improve this test after only three days (8). The mechanism may be enhanced NO production and its chronic delivery to the muscularis from the endothelium. Statin treatment in the cholesterol fed rabbit has been associated with increased synthesis of eNOS independent of plasma cholesterol (12). In vitro experiments have found a prolonged survival of the mRNA for eNOS and an associated enhancement of translation into the protein (13,14). NO survival may also be enhanced by statins through reduction in destructive superoxide anion. The activity of the enzyme thought to be the major source of superoxide, NADPH oxidase, has been reported to be suppressed after cells are exposed to atorvastatin (15). This statin was also found to increase the translation of an important antioxidant enzyme, catalase. These studies suggest a

direct effect of the simvastatin on the endothelium causing an increase in NO. However, the LDL cholesterol fell by 35% in these experiments, and direct reduction of LDL by physical removal by column-based lipophoresis has also been shown to improve endothelial function immediately in subjects with familial hypercholesterolemia and endothelial dysfunction (16).

Our study differs in that this compliance measure is not an acute response to a stimulus that is purported to release NO but one that reflects a more chronic state of the arterial wall. Pulse velocity (an indicator of reduced compliance) in sheep femoral arteries has been shown to respond to nitroglycerin and decrease with inhibitors of NO release (LNMMA)(17). Studies of arterial compliance in the human brachial artery using intravascular ultrasound have demonstrated a similar control mechanism (18,19). In certain muscular arteries, it thus seems highly likely that there is a chronic state of increased tone in active arteriosclerosis that is NO dependent and responsive to those interventions which would allow the endothelium to release NO in a more continuous manner.

We believe a placebo-controlled study was not ethical in these patients. We therefore documented stability of the measure in similar patients on or off stable statin therapy during the same time period using the same machines. Three measures performed on different days over one month showed no trend in groups of men and women who were taking statins and in comparable groups who had not taken statins for months.

The lack of any measurable change in compliance in the arteries of the calf after beginning simvastatin therapy is puzzling in view of the dramatic and consistent response of those in the thigh. The large arteries of the calf may be less responsive to NO or the compliance in this vascular field may be more dependent on connective tissue elements that would not be expected to change in the period of this study. Baseline compliance in the thigh was significantly reduced when the MaxV50 of the eight men in this study was compared to men with no evident CAD and one or fewer risk factors. At the end of the study, four of the ten patients had values in the normal range. In contrast, the calf measures in these men were within the normal range at baseline suggesting that significant sclerotic disease was not the reason for lack of responsiveness to the simvastatin treatment. Even though compliance did improve in the thigh arteries in all these patients, the values were still abnormal in six patients at the end of the study. Longer periods of therapy have been shown to improve aortic compliance, an artery with relatively greater quantities of collagen (3,4,5). This study suggests that an accurate and stable measure of muscular artery compliance in the thigh may provide an assessment tool to document improved vascular physiology in patients given effective treatment for causative risk factors in arteriosclerotic vascular disease.

Acknowledgements

This work was supported in part by a grant from Merck Co., Inc., West Point, Pennsylvania and by a grant and the provision of the Vasogram Device by the Vasocor Corporation of Charleston, SC.

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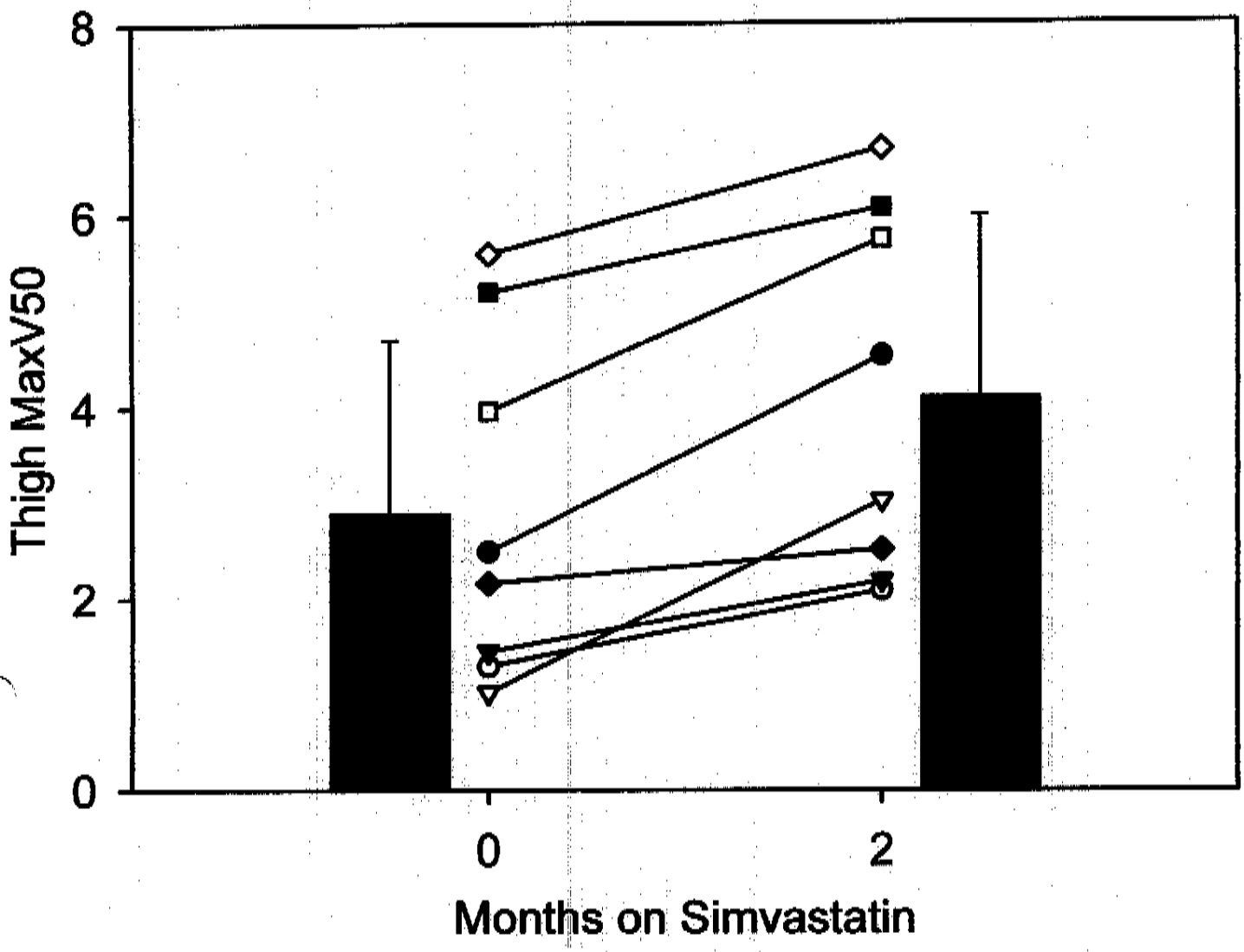
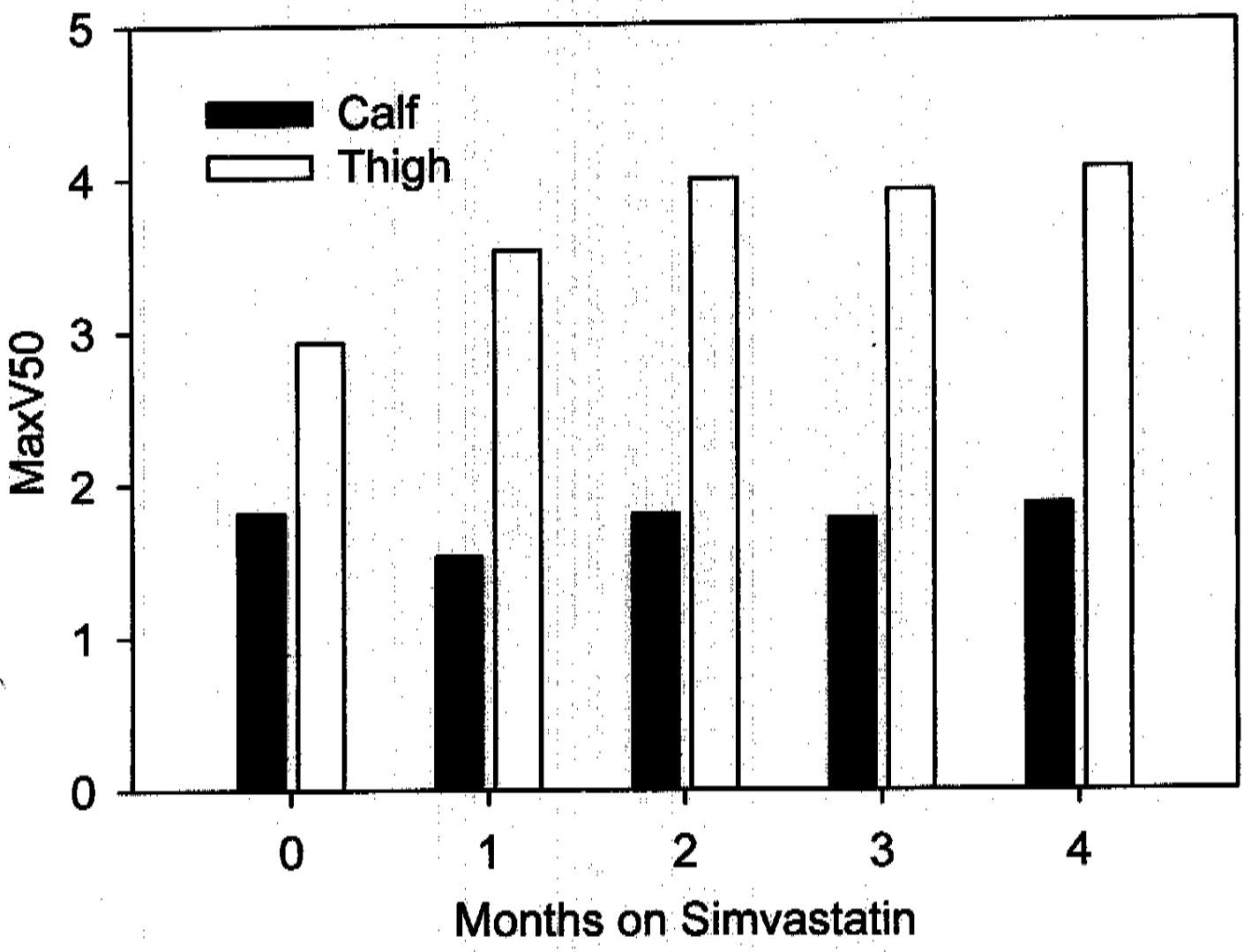
Figure Legends

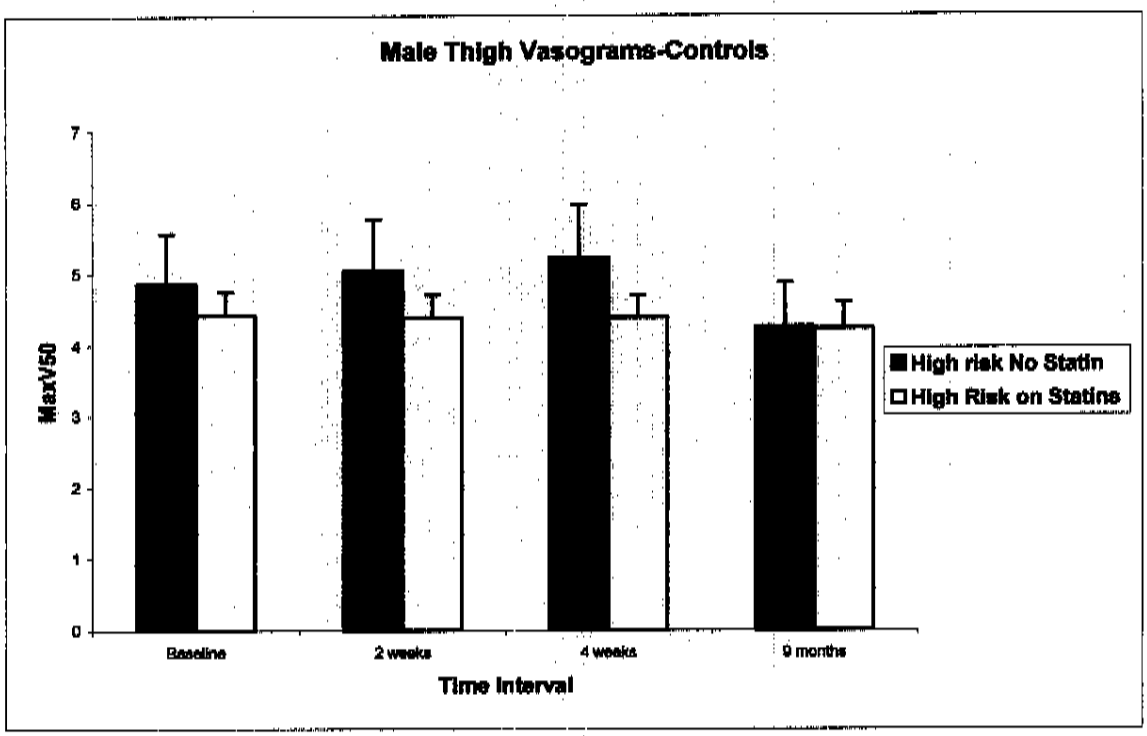
Figure 1. Thigh compliance MaxV50 at baseline and after 2 months of simvastatin in the 10 patients is plotted with individual values and the bar graph shows mean values ± sd.

Figure 2. MaxV50 at baseline and during the four months of the study is plotted for thigh and calf.

Figure 3. MaxV50 at the thigh is plotted in a group of contemporaneous control subjects that were on no statin therapy or on stable long-term statin therapy. The bar graph shows mean values ± sd.


8
6
4
2
0
Thigh MaxV50
0
2
Months on Simvastatin


Calf
Thigh
MaxV50
0
1
2
3
4
5
0
1
2
3
4
Months on Simvastatin


Male Thigh Vasograms-Controls
MaxV50
0
1
2
3
4
5
6
7
Baseline
2 weeks
4 weeks
9 months
Time Interval
High risk No Statin
High Risk on Statins