Intensive Cholesterol Reduction Lowers Blood Pressure and Large Artery Stiffness in Isolated Systolic Hypertension

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OBJECTIVES
We sought to investigate the effects of intensive cholesterol reduction on large artery stiffness and blood pressure in normolipidemic patients with isolated systolic hypertension (ISH).

BACKGROUND
Isolated systolic hypertension is associated with elevated cardiovascular morbidity and mortality and is primarily due to large artery stiffening, which has been independently related to cardiovascular mortality. Cholesterol-lowering therapy has been efficacious in reducing arterial stiffness in patients with hypercholesterolemia, and thus may be beneficial in ISH.

METHODS
In a randomized, double-blinded, cross-over study design, 22 patients with stage I ISH received three months of atorvastatin therapy (80 mg/day) and three months of placebo treatment. Systemic arterial compliance was measured noninvasively using carotid applanation tonometry and Doppler velocimetry of the ascending aorta.

RESULTS
Atorvastatin treatment reduced total and low-density lipoprotein cholesterol and triglyceride levels by 36 ± 2% (p < 0.001), 48 ± 3% (p < 0.001) and 23 ± 5% (p = 0.003), respectively, and increased high density lipoprotein cholesterol by 7 ± 3% (p = 0.03). Systemic arterial compliance was higher after treatment (placebo vs. atorvastatin: 0.36 ± 0.03 vs. 0.43 ± 0.05 ml/mm Hg, p = 0.03). Brachial systolic blood pressure was lower after atorvastatin treatment (154 ± 3 vs. 148 ± 2 mm Hg, p = 0.03), as were mean (111 ± 2 vs. 107 ± 2 mm Hg, p = 0.04) and diastolic blood pressures (83 ± 1 vs. 81 ± 2 mm Hg, p = 0.04). There was a trend toward a reduction in pulse pressure (71 ± 3 vs. 67 ± 2 mm Hg, p = 0.08).

CONCLUSIONS
Intensive cholesterol reduction may be beneficial in the treatment of patients with ISH and normal lipid levels, through a reduction in large artery stiffness. (J Am Coll Cardiol 2002; 39:1020–5) © 2002 by the American College of Cardiology Foundation

Isolated systolic hypertension (ISH) affects 26% of the population >55 years (1), is associated with coronary and cerebrovascular events (2–5) and arises as a result of large artery stiffening (6–8). Although antihypertensive drug therapy reduces the occurrence of fatal and nonfatal events (9), large reductions in diastolic blood pressure (DBP) may potentially contribute to myocardial ischemia (10). Furthermore, although antihypertensive drugs may reduce arterial stiffness through a passive effect, few have a proven effect on the arterial structure (11).

Cholesterol lowering is an alternative therapy that may potentially target arterial stiffness, and thus blood pressure, through effects on endothelial function and arterial wall composition. A number of studies in hypercholesterolemic patients have shown improvement, particularly in peripheral artery properties, with cholesterol-lowering therapy (12–16). It is unknown whether a cholesterol reduction within the normal clinical range in patients with ISH might also reduce stiffness of the large arteries, and thereby systolic blood pressure (SBP). In a randomized, cross-over design, the current study sought to examine the effects of three months of intensive cholesterol reduction with atorvastatin (80 mg/day) on large artery stiffness and blood pressure in patients with stage I ISH.

METHODS
All participants gave informed consent to participate in the study, which was undertaken with the approval of the Alfred Healthcare Group Ethics Committee and carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Subjects. Twenty-two patients with stage I ISH (18 men and 4 women; mean age ± SD; 60 ± 14 years) were recruited. Inclusion criteria for stage I ISH were a clinic SBP >140 mm Hg, but <170 mm Hg, and DBP <90 mm Hg. Exclusion criteria were age >80 and <18 years, low density lipoprotein (LDL) cholesterol <2.5 mmol/l, antihypertensive therapy, use of vasoactive or cholesterol-lowering medication, excess alcohol consumption (>4 standard drinks/day), smoking, coronary artery disease (based
on history and examination) and other major medical illness. None of the female participants were taking hormone replacement therapy.

**Study design.** At baseline, all patients had measurements of rest (supine) blood pressure, systemic arterial compliance (SAC), fasting lipid profile and cardiac structure and function (by echocardiography). In a double-blinded, randomized, cross-over study design, patients received three months of treatment with placebo and three months of therapy with atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin), at a dose of 80 mg/day. All measurements, except for echocardiographic ones, were repeated in the morning after an overnight fast at three and six months.

**Cardiac structure and function.** Indexes of cardiac structure and function were assessed at baseline only. Left ventricular end-diastolic posterior wall thickness, interventricular septal wall thickness at end diastole, left ventricular internal end-diastolic diameter (LVIDD) and left ventricular internal end-systolic diameter (LVVIDS) were measured using the American Society of Echocardiography convention from M-mode images of the left ventricle, generated in the short-axis view at the level of the mitral chordae. Using these measurements, left ventricular mass (LVM), normalized for body surface area (LVM index), was estimated (17). Left ventricular systolic function was assessed as fractional shortening (FS), where

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FS = 100 \times (LVIDD - LVVIDS) / LVIDD
\]

**Rest blood pressure and heart rate.** Three brachial artery blood pressure measurements and three heart rate measurements were made at 3-min intervals with the use of a Dinamap vital signs monitor (1846 SX Critikon, Tampa, Florida), with the subjects remaining in the supine position in a darkened, quiet room. The mean of these three values was taken to represent the rest level.

**Systemic arterial compliance.** This was determined using the method of Liu et al. (18) and validated in our laboratory by Cameron and Dart (19). This method requires measurement of carotid artery pressure byplanation tonometry, using a Millar Mikro-Tip pressure transducer (SPT-301, Millar Instruments, Houston, Texas), and volumetric aortic flow (cardiac output), using a hand-held, continuous wave Doppler velocimeter with a 3.5-MHz transducer (Multi-Dopplex MD1, Huntleigh Technology, Cardiff, United Kingdom), as well as two-dimensional echocardiography for assessment of the left ventricular outflow tract area. Brachial artery pressure was obtained simultaneously with a Dinamap monitor and used to calibrate the carotid artery pressure contour using diastolic and mean pressures (19).

**Biochemical analyses.** A 30-ml blood sample was taken at baseline and after each intervention for enzymatic analysis of plasma total, LDL and high-density lipoprotein (HDL) cholesterol, triglycerides and glucose, using a Cobas-Fara centrifugal analyzer (Roche Diagnostic Systems, Basel, Switzerland).

**Statistics.** All data are presented as the mean value ± SEM, unless otherwise stated. All variables were compared using two-way analysis of variance for repeated measures to examine the effects of treatment (p treatment) and order of intervention (p order) and treatment–order interaction (p interaction). All statistical analyses were performed using SPSS, version 10.0 (SPSS Inc., Chicago, Illinois).

**RESULTS**

The average age and body mass index of the participants were 60 ± 3 years and 28 ± 1 kg/m², respectively (height 174 ± 2 cm; weight 83 ± 2 kg). Indexes of cardiac structure and function, including left ventricular mass (182 ± 9 g), left ventricular mass index (93 ± 4 g/m²) and fractional shortening (38 ± 1%), were all within normal ranges. Plasma glucose levels did not change with treatment (Table 1). After treatment with atorvastatin, plasma total and LDL cholesterol and triglyceride levels were reduced, whereas HDL cholesterol was increased, as compared with placebo (Table 1). In addition to being reduced by atorvastatin treatment, triglyceride levels were also significantly reduced.

**Table 1.** Effects of Atorvastatin Therapy on Lipids and Glucose

<table>
<thead>
<tr>
<th>Variable</th>
<th>After Placebo</th>
<th>After Atorvastatin</th>
<th>p treatment</th>
<th>p order</th>
<th>p interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.46 ± 0.21</td>
<td>3.46 ± 0.12</td>
<td>&lt;0.001</td>
<td>0.91</td>
<td>0.05</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.40 ± 0.16</td>
<td>1.77 ± 0.10</td>
<td>&lt;0.001</td>
<td>0.96</td>
<td>0.12</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.13 ± 0.06</td>
<td>1.21 ± 0.06</td>
<td>0.03</td>
<td>0.31</td>
<td>0.47</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.38 ± 0.13</td>
<td>1.00 ± 0.08</td>
<td>0.003</td>
<td>0.002</td>
<td>0.68</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.65 ± 0.30</td>
<td>5.28 ± 0.17</td>
<td>0.11</td>
<td>0.52</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SEM. *P* values are presented for the effects of treatment (*p* treatment), order (*p* order) and the interaction between treatment and order (*p* interaction).

LDL = low-density lipoprotein; HDL = high-density lipoprotein.
After atorvastatin treatment, SAC was increased by 24 \% (p_treatment = 0.03, p_order = 0.48, p_interaction = 0.98). Data are presented as the mean value ± SEM.

with time (p_order = 0.002) (Table 1). Cholesterol reduction was greater in those who received atorvastatin second (p_interaction = 0.05) (Table 1). There was no effect of the order of intervention, nor any treatment–order interaction, for any other variable.

### Systemic arterial compliance and hemodynamic data.

After atorvastatin treatment, SAC was increased by 24 ± 9\% (p_treatment = 0.03, p_order = 0.48, p_interaction = 0.98) (Fig. 1). Rest SBP of the brachial artery was reduced by 6 ± 2 mm Hg (p_treatment = 0.03, p_order = 0.62, p_interaction = 0.76) after atorvastatin treatment, while DBP and mean arterial pressure (MAP) were reduced by 2 ± 1 mm Hg (p_treatment = 0.04, p_order = 0.19, p_interaction = 0.42) and 4 ± 2 mm Hg (p_treatment = 0.04, p_order = 0.79, p_interaction = 0.99), respectively (Fig. 2). There was a trend toward reduced pulse pressure (placebo vs. atorvastatin: 71 ± 3 vs. 67 ± 2 mm Hg; p_treatment = 0.08, p_order = 0.20, p_interaction = 0.44). The rest heart rate was not different between placebo and atorvastatin treatment (64 ± 2 vs. 64 ± 2 beats/min; p_treatment = 0.83, p_order = 0.45, p_interaction = 0.12). Total peripheral resistance (TPR) was reduced after atorvastatin treatment (22.8 ± 1.8 vs. 18.9 ± 1.4 \Omega \cdot \text{m}^2 \cdot \text{m}^{-3} \cdot \text{s}^{-1} \cdot \text{mmHg}^{-1}; p_treatment = 0.05, p_order = 0.15, p_interaction = 0.73), although there was no change in cardiac output (p_treatment = 0.12, p_order = 0.67, p_interaction = 0.57). In addition, blood pressure and heart rate were not different when taken during measurement of SAC (data not shown).

### Safety variables.

At baseline, three patients had plasma alanine aminotransferase (ALT) levels above the normal upper limit of 40 U/l, but all patients had aspartate aminotransferase (AST) levels below the normal upper limit of 50 U/l. After atorvastatin treatment, versus placebo, there was a significant rise in both ALT (27 ± 3 vs. 42 ± 6 U/l; p_treatment = 0.05, p_order = 0.53, p_interaction = 0.35) and AST (24 ± 1 vs. 30 ± 3 U/l; p_treatment = 0.05, p_order = 0.08, p_interaction = 0.30). Treatment increased ALT levels above 40 U/l in seven patients and AST levels above 50 U/l in two patients, but no patient was beyond three times the normal range. No patient complained of myalgia.

### DISCUSSION

Intensive cholesterol reduction with atorvastatin (80 mg/day) over three months reduced large artery stiffness and blood pressure in normocholesterolemic patients with stage I ISH. Total and LDL cholesterol and triglyceride levels were reduced to a similar extent, as reported in hypercholesterolemic patients (20,21), and HDL cholesterol was significantly increased by treatment. As ISH is a condition characterized by the presence of stiffened arteries (6–8), cholesterol-lowering therapy may slow progression. Furthermore, a reduction of large artery stiffness may contribute to the long-term benefits of statins, with regard to the risk of coronary events and stroke (22).

Blood pressure reduction has not previously been reported with intensive cholesterol reduction in normallipidemic patients. Furthermore, blood pressure reduction does not occur with statin treatment in hypercholesterolemic, normotensive patients (13,16,23–25). In patients with controlled hypertension who were also hypercholesterolemic, two studies found no change in blood pressure levels with additional statin treatment (26,27), whereas others demonstrated that additional statin therapy led to a greater reduction in SBP, MAP and DBP (28,29). Collectively, this suggests that statins may be more effective in lowering elevated, but not normal, blood pressure levels, regardless of cholesterol levels.

In the current study, a reduction in large artery stiffness probably underlies the reduced SBP and trend for reduced pulse pressure, however MAP fell slightly due to a reduction...
in TPR. As arterial stiffness is dependent on MAP (18), any reduction in MAP leads to a passive decrease in arterial stiffness, and thus may partly account for the observed arterial compliance changes. However, the reduction in MAP was small, and it is likely that the passive reduction in stiffness was also minimal, implying that atorvastatin also had direct effects on the arterial wall.

Previous studies have found that cholesterol-lowering therapy reduces arterial stiffness in the descending aorta (14) and carotid (13), femoral (12,13) and brachial (16) arteries of patients with familial hypercholesterolemia. Interestingly, only studies in which cholesterol-lowering therapy was taken for ≥12 months reported a reduction in arterial stiffness (13,14,16,23), as compared with a shorter six-month intervention study examining brachial artery stiffness (25). In nonfamilial hypercholesterolemic patients, four weeks of cholesterol-lowering therapy failed to alter central and carotid, femoral or brachial (16) arteries stiffness. The shorter period in which alterations were observed in the current study may be due to the different patient group, which, besides having higher blood pressure and stiff large arteries, had relatively normal cholesterol levels. Atorvastatin was also used at a maximal dose in the current study, and at this dose, it has greater efficacy for LDL reduction, as compared with pravastatin or simvastatin (20), which were used in some of the shorter trials (15,24,25).

Mechanisms. Large artery stiffening in patients with ISH may relate to alterations in the extracellular matrix, changes in smooth muscle content, endothelial injury and atherosclerotic lesion formation. Favorable alterations in any of these variables could bring about improvements in arterial stiffness.

The rapid time frame for the observed pressure and arterial compliance changes is compatible with changes in endothelial function, which is improved with cholesterol-lowering therapy in patients with hypercholesterolemia (30), hypertriglyceridemia (31) and coronary artery disease (32,33) and in those who have had acute coronary syndromes (34). Benefits occur quickly, with one study reporting improvements after four weeks of therapy (35). Statins increase the availability of nitric oxide through an increase in endothelial nitric oxide synthase activity and expression (36,37) and also inhibit endothelin-1 production (38). The consequent vasodilation that occurs with an improvement in endothelial function may contribute to the reduction in MAP, and hence indirectly to the increase in arterial compliance. In addition, improved endothelial function in both the aorta and vasa vasorum (39) may directly affect large artery stiffness.

Atherosclerotic regression has been associated with improvement in arterial stiffness (40), raising the possibility that atorvastatin may modify aortic atherosclerotic lesions. Statin therapy for as little as eight weeks causes atherosclerotic plaque modification in rabbits (41–44). A reduction in platelet deposition and nitric oxide–mediated leukocyte rolling, adherence and transmigration, all the result of statin treatment, may contribute to plaque stabilization and regression (45,46). A reduction in matrix metalloproteinase expression may also contribute, because these enzymes are secreted by atheromatous cells and have been implicated in the weakening of the fibrous cap in unstable plaques (47). Statin treatment reduces matrix metalloproteinase expression in human carotid plaques (48) and rabbit aortic atheroma (49), and may therefore inhibit degradation of the elastic matrix and decrease stiffness.

Study implications. Patients with ISH who have stiff large arteries are at an elevated risk for stroke and coronary events. The risk for the latter relates to both elevated cardiac afterload (50) and promotion of left ventricular hypertrophy (51), in addition to restricted coronary perfusion arising from low diastolic pressure (52,53). The current data indicate that in normolipidemic patients with ISH, intensive lipid-lowering therapy for three months has efficacy in targeting large artery stiffness, which is the underlying cause of ISH. Such therapy may be beneficial in slowing the progression of ISH and reducing coronary disease-associated risk. Larger clinical trials are warranted to confirm these data.

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