Not Acute but Chronic Hypertriglyceridemia Is Associated With Impaired Endothelium-Dependent Vasodilation
Reversal After Lipid-Lowering Therapy by Atorvastatin

Frits H. de Man, Annelies W.E. Weverling-Rijnsburger, Arnoud van der Laarse, Augustinus H.M. Smelt, J. Wouter Jukema, Gerard J. Blauw

Abstract—There is controversy regarding the relation between hypertriglyceridemia (HTG) and endothelial function. This study was designed to investigate endothelial function in a patient group with chronic HTG, before and during lipid-lowering therapy by atorvastatin. In addition, the effects of acute HTG on endothelial function were studied in normolipidemic individuals. Eight male patients with chronic HTG were studied before and after 6 weeks of lipid-lowering treatment with 80 mg atorvastatin once daily. Ten age-matched control subjects were studied at baseline and immediately after a high-dose infusion of artificial triglycerides. The endothelium-dependent response to serotonin was attenuated in the HTG group, whereas the response to acetylcholine was comparable to the response in the control group. The response to the endothelium-independent vasodilator nitroprusside was comparable in both groups. In response to atorvastatin therapy, serum triglyceride and cholesterol levels decreased significantly by 43% (paired t test, P=0.017) and 38% (paired t test, P=0.012), respectively. After 6 weeks of treatment, the forearm blood flow response to serotonin improved from 63% to 106% (ANOVA, P<0.001). Induction of acute HTG in the control subjects did not affect the forearm blood flow responses to serotonin and nitroprusside; however, the response to acetylcholine was paradoxically increased. In conclusion, patients with chronic HTG have an impaired endothelium-dependent vasodilation to serotonin that is normalized after 6 weeks of lipid-lowering therapy by atorvastatin. (Arterioscler Thromb Vasc Biol. 2000;20:744-750.)

Key Words: endothelium • hyperlipoproteinemia • triglycerides

Endothelial dysfunction is regarded as an early feature of atherosclerosis. Most cardiovascular risk factors, like hypercholesterolemia, smoking, hypertension, and age, have been shown to be associated with an impaired endothelium-dependent vasodilation.¹⁻⁵ However, the effects of hypertriglyceridemia (HTG) on endothelial function are still subject to discussion. Incubation of aortic rings with triglyceride-rich lipoproteins inhibited the endothelium-dependent vasodilation to the same extent as LDLs did.⁶ In accordance, oral as well as intravenous triglyceride loads in healthy subjects induced an impaired endothelial response within hours.⁷⁻⁸ In sharp contrast to this concept, Chowienczyk et al⁹ showed normal endothelium-dependent responsiveness to acetylcholine in patients with severe HTG. The present study was designed to investigate endothelial function in a group of patients with chronic HTG and to evaluate the effects of lipid-lowering therapy by atorvastatin. In addition, the acute effects of HTG, induced by intravenous infusion of artificial triglycerides, on endothelial function were studied in healthy normolipidemic subjects.

Methods

Subjects
The study population included 8 patients with chronic HTG (Fredrickson types IV and V) and 10 healthy normolipidemic control subjects. The patients with HTG were recruited from the outpatient lipid clinic of the Leiden University Medical Center. Patients with HTG were eligible if they had a total serum triglyceride >4.0 mmol/L, VLDL cholesterol >1.0 mmol/L, and LDL cholesterol <4.5 mmol/L on 2 separate occasions under fasting conditions. Exclusion criteria were the apoE2E2 phenotype, secondary hyperlipidemia (renal, liver, or thyroid disease; fasting glucose >7.0 mmol/L; and alcohol consumption >40 g/d), and the use of lipid-lowering drugs. All individuals were nonsmoking, normotensive, and without history of cardiovascular disease. The HTG group had a mean postheparin lipoprotein lipase (LPL) activity that was the same order of magnitude as found in the control group (Table). The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center, and all subjects gave informed consent.

Biochemistry
Venous blood was collected after an overnight fast. Serum was obtained after centrifugation at 1500g for 15 minutes at room temperature and stored at -80°C until analyses were performed. Venous blood samples were drawn at baseline and immediately after a high-dose infusion of artificial triglycerides.

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temperature. Three milliliters of fresh serum was ultracentrifuged for 15 hours at 232 000g at 15°C. The resultant was carefully divided into fractions at a density <1.006 g/mL and a density of 1.006 to 1.25 g/mL, designated as the VLDL and LDL+HDL fractions, respectively. HDL cholesterol was measured in the LDL+HDL fraction after precipitation of apoB-containing particles with phosphotungstic acid and MgCl2. Triglyceride, cholesterol, and free fatty acid concentrations were measured enzymatically by using commercially available kits. ApoB and apoA-I were assessed by a turbidimetric assay. LDL cholesterol was measured in the LDL-HDL fraction after precipitation of apoB-containing particles with phosphotungstic acid and MgCl2, respectively. HDL cholesterol was measured in the LDL-HDL fraction. FFA, free fatty acids; and LPL, postheparin LPL activity. To convert mmol/L cholesterol to mg/dL, multiply by 38.7; to convert mmol/L triglycerides to mg/dL, multiply by 88.5.

<table>
<thead>
<tr>
<th>Study Groups and Effects of Atorvastatin Therapy in Patients</th>
<th>Control Subjects</th>
<th>HTG Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46±7</td>
<td>51±9</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>55.9±2.9</td>
<td>68.3±5.4</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>126.8±4.7</td>
<td>121.5±4.4</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>61.6±4.2</td>
<td>52.3±2.1</td>
</tr>
<tr>
<td>Baseline FBF, mL · 100 mL⁻¹ · min⁻¹</td>
<td>2.25±0.26</td>
<td>2.69±0.27</td>
</tr>
<tr>
<td>TTG, mmol/L</td>
<td>0.80±0.11</td>
<td>12.05±4.02</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>4.85±0.35</td>
<td>7.83±1.55</td>
</tr>
<tr>
<td>VLDL-C, mmol/L</td>
<td>0.18±0.03†</td>
<td>4.72±1.53</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>3.29±0.30‡</td>
<td>2.42±1.16</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.38±0.09*</td>
<td>0.70±0.06</td>
</tr>
<tr>
<td>ApoA-I, g/L</td>
<td>1.30±0.05†</td>
<td>1.09±0.04</td>
</tr>
<tr>
<td>ApoB, g/L</td>
<td>1.01±0.07</td>
<td>1.10±0.12</td>
</tr>
<tr>
<td>FFA, mmol/L</td>
<td>0.53±0.06‡</td>
<td>1.02±0.32</td>
</tr>
<tr>
<td>LPL, U/L</td>
<td>158±10</td>
<td>223±66</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; TTG, total triglycerides; TC, total cholesterol; VLDL-C, VLDL cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; FFA, free fatty acids; and LPL, postheparin LPL activity. To convert mmol/L cholesterol to mg/dL, multiply by 38.7; to convert mmol/L triglycerides to mg/dL, multiply by 88.5.

n=10 for controls; n=8 for HTG patients. *P<0.001, †P<0.01, and ‡P<0.05 for controls vs HTG patients at baseline (nonpaired t test). §P<0.05 and ¶P<0.01 for HTG patients at baseline vs HTG patients after atorvastatin therapy (paired t test).

Procedures

All subjects were studied under fasting conditions in a quiet room and were instructed to avoid excessive physical activity the day of the study and store food at 4°C until use. Atorvastatin was used as the reference drug; all other drugs were given in a randomized order, and each dose was given over a 20-minute period. The drugs were given in a randomized order, and each dose was given over a 20-minute period. The drugs were given in a randomized order, and each dose was given over a 20-minute period. The drugs were given in a randomized order, and each dose was given over a 20-minute period. The drugs were given in a randomized order, and each dose was given over a 20-minute period.

For forearm blood flow (FBF) was measured by computerized, R wave-triggered, venous occlusion plethysmography with the use of mercury in silastic strain gauges and a rapid cuff inflator (Hokanson Inc) as described previously.11 During the measurements of FBF, the hand was excluded from the circulation by use of a small wrist cuff inflated to 40 mm Hg above the systolic blood pressure. Endothelial-dependent vasodilation was determined during cumulative-dose infusions of acetylcholine (30 and 90 ng · kg⁻¹ · min⁻¹) and serotonin (0.3 and 0.9 ng · kg⁻¹ · min⁻¹). Sodium nitroprusside (30 and 90 ng · kg⁻¹ · min⁻¹) was infused as an endothelium-independent vasodilator. The drugs were given in a randomized order, and each dose was given over a 20-minute period. The drugs were given in a randomized order, and each dose was given over a 20-minute period. The drugs were given in a randomized order, and each dose was given over a 20-minute period.

Drugs and Solutions

The following compounds were used for intra-arterial infusions: acetylcholine HCl (Ciba Vision Opta), 5-hydroxytryptamine HCl (ICN Pharmaceuticals), sodium nitroprusside (Merck), and L-arginine (Bufa BV). All drugs were dissolved in 0.9% saline, except for nitroprusside, which was dissolved in 5% glucose. Intralipid (20% fat emulsion, Pharmacia and Upjohn) was used as artificial triglyceride emulsion for intravenous administration. The solutions were prepared from sterile stock solutions and ampoules on the day of the study and stored at 4°C until use. Atorvastatin (Lipitor) tablets of 40 mg were provided by Parke-Davis (Hooifddorp, the Netherlands).

Study Protocol

HTG Patients

The patients with chronic HTG were studied on 2 separate occasions: at baseline and after 6 weeks of treatment with atorvastatin 80 mg...
once daily. At each occasion, FBF responses to acetylcholine, serotonin, and nitroprusside were assessed during simultaneous infusions of saline and L-arginine in a dose of 0.2 mg · kg⁻¹ · min⁻¹. The order of drug administration was randomized. Saline and L-arginine infusions were started 5 minutes before the start of the acetylcholine, serotonin, and nitroprusside infusions. Drug compliance was assessed by tablet counting.

**Control Subjects**
The control subjects were studied before and during the induction of an acute systemic HTG. After assessment of the baseline FBF responses to the intra-arterial infusions of serotonin and nitroprusside, a cannula was inserted in an antecubital vein of the contralateral arm. Subsequently, a bolus of 0.25 g · kg⁻¹ Intralipid was administered for 2 minutes, followed by a graded infusion at a dose of 0.40 g · kg⁻¹ · min⁻¹. Immediately after reaching a stable level of HTG, the intra-arterial infusions of acetylcholine, serotonin, and nitroprusside were repeated and completed within 70 minutes after the onset of acute HTG. To assess the effects of the Intralipid infusions on the lipoprotein profile, blood samples of 3 representative subjects were drawn before and at the end of the Intralipid administration. Then, the plasma lipoproteins in these samples were isolated by ultracentrifugation according to Redgrave et al. L-Arginine infusions were not performed in the control subjects, because previous studies have demonstrated that L-arginine does not increase endothelium-dependent vasodilation in healthy subjects.

**Statistical Methods**
Values are expressed as mean ± SEM. Comparisons between groups were evaluated by Student nonpaired 2-tailed t test and ANOVA. Effects of atorvastatin therapy were analyzed by Student paired 2-tailed t test and repeated-measures ANOVA. Analysis of triglyceride levels was performed on logarithmically transformed data. Statistical significance was accepted at the 95% confidence level. The statistical analyses were performed with SPSS/PC+ software (SPSS Inc).

**Results**

**Baseline Characteristics**
The Table provides characteristics of the study groups. All subjects were normotensive, nondiabetic, nonsmoking males. There were no significant differences in age. The HTG group demonstrated 15-fold higher serum triglyceride levels than did the control group. Also, the serum cholesterol levels were elevated because of the high VLDL levels in the patient group. The HDL cholesterol and LDL cholesterol concentrations were lower than in the control group. Interestingly, free fatty acid levels were elevated in the HTG group, whereas postheparin LPL activities were of the same order of magnitude as found in the control group.

**Lipids and Lipoproteins**

**Atorvastatin Therapy**
In accordance with previous studies, atorvastatin therapy at a dose of 80 mg once daily induced a major improvement of the lipoprotein profile in patients with chronic HTG. As shown in the Table, serum triglyceride and cholesterol levels decreased considerably within 6 weeks of treatment. The main lipid-lowering effects were observed in the VLDL and LDL fractions.

**Artificial HTG**
The systemic intravenous infusion of Intralipid resulted in a rapid 15-fold increase in serum triglycerides to levels that remained stable during the graded infusion scheme (Figure 1A). Total serum cholesterol levels did not change, whereas free fatty acid levels increased significantly from 0.29 to 1.65 mmol/L after 70 minutes. Analysis of the lipoprotein cholesterol profiles, before and during this acute HTG, demonstrated that the LDL and HDL fractions were not affected (Figure 1B). The corresponding lipoprotein triglyceride profiles showed a sharp peak in the region with a density <1.006 g/mL, indicative of artificial chylomicronemia, whereas the LDL and HDL fractions were not affected (data not shown). These results indicate that an acute and stable HTG has been established without affecting the other lipoprotein fractions up to 70 minutes after the start of the Intralipid infusion.

**Hemodynamic Measurements**
The local intra-arterial infusions of acetylcholine, serotonin, sodium nitroprusside, and L-arginine did not induce any significant changes in intra-arterial blood pressure and heart rate (data not shown). Therefore the FBF changes can be
interpreted as local vascular effects of the vasoactive substances used.\textsuperscript{11}

**Vascular Responses at Baseline**

The cumulative dose infusions of acetylcholine, serotonin, and nitroprusside induced a significant dose-dependent vasodilation in both study groups (Figure 2). The FBF responses to acetylcholine were comparable in the control and HTG groups: 69$\pm$13\% versus 59$\pm$15\% at the highest dose, respectively (ANOVA, $P=0.59$; Figure 2A). The concomitant infusion of L-arginine in the HTG group increased the vasodilator responses to acetylcholine from 59$\pm$15\% to 122$\pm$28\% at the highest dose (repeated-measures ANOVA, $P=0.009$). At baseline, the FBF responses to serotonin were significantly lower in the HTG group than in the control group: 63$\pm$10\% versus 103$\pm$10\% at the highest dose, respectively (ANOVA, $P=0.001$; Figure 2B). The concomitant infusion of L-arginine in the HTG group significantly improved the vasodilator responses to serotonin from 63$\pm$10\% to 113$\pm$9\% at the highest serotonin dose (repeated-measures ANOVA, $P<0.001$). The FBF responses to the endothelium-independent vasodilator nitroprusside were comparable in the HTG patients and control subjects, as is shown in Figure 2C. At the highest dose, the FBF was 292$\pm$42\% in the HTG group versus 348$\pm$42\% in the reference group (ANOVA, $P=0.14$). The infusion of L-arginine did not alter the FBF responses to nitroprusside (repeated-measures ANOVA, $P=0.92$).

**Vascular Responses After Atorvastatin Therapy**

After 6 weeks of atorvastatin therapy at a dose of 80 mg once daily, the vasodilator responses to acetylcholine were not affected (Figure 3A). At the highest dose of acetylcholine, the FBF response was 66$\pm$25\% after atorvastatin therapy compared with 59$\pm$15\% at baseline (repeated-measures ANOVA, $P=0.88$). Coinfusion with L-arginine did improve the vasodilator responses to serotonin from 63$\pm$10\% to 113$\pm$9\% at the highest serotonin dose (repeated-measures ANOVA, $P<0.001$). The FBF responses to the endothelium-independent vasodilator nitroprusside were comparable in the HTG patients and control subjects, as is shown in Figure 2C. At the highest dose, the FBF was 292$\pm$42\% in the HTG group versus 348$\pm$42\% in the reference group (ANOVA, $P=0.14$). The infusion of L-arginine did not alter the FBF responses to nitroprusside (repeated-measures ANOVA, $P=0.92$).
dilator responses to acetylcholine significantly to 110 ± 15% at the highest dose (repeated-measures ANOVA, P = 0.013). However, compared with baseline responses, the vasodilator responses to serotonin were significantly improved by atorvastatin therapy (Figure 3B). The maximum increase in FBF was 106 ± 7% at the highest dose (repeated-measures ANOVA, P < 0.001). After atorvastatin treatment, the infusion of l-arginine compared with the saline coinfusion did not influence vasodilator effects of serotonin (repeated-measures ANOVA, P = 0.43; Figure 3B). The FBF responses to nitroprusside did not change significantly after atorvastatin therapy, although there was a tendency toward an increased FBF response compared with the FBF response to nitroprusside at baseline (repeated-measures ANOVA, P = 0.052; Figure 3C).

Compared with saline, the infusion of L-arginine did not influence the vasodilator effects of nitroprusside (repeated-measures ANOVA, P = 0.10).

**Vascular Responses During Acute HTG**

Immediately after the establishment of HTG in control subjects, the FBF measurements were carried out with a randomly chosen order of the acetylcholine, serotonin, and nitroprusside infusions. As shown in Figure 4, the FBF responses to serotonin and nitroprusside were not affected by the systemic Intralipid infusion. During this artificial HTG, the FBF responses to the highest doses of serotonin and nitroprusside were 117 ± 21% and 409 ± 67%, respectively, compared with 103 ± 10% (repeated-measures ANOVA, P = 0.97) and 348 ± 42% (repeated-measures ANOVA, P = 0.47), respectively, before the triglyceride infusion. Unexpectedly, we observed an increased FBF response to acetylcholine during the artificial HTG. At the highest acetylcholine dose, the FBF response was 180 ± 36% during HTG compared with 69 ± 13% during the saline infusion (repeated-measures ANOVA, P = 0.021).

**Discussion**

The main finding of the present study is the association of chronic HTG with a selective loss of endothelial function as measured by exogenously administered serotonin in the human forearm. The fact that the HTG patients participating in the present study were free from other cardiovascular risk factors or any other disease strongly suggests that HTG is the cause of this endothelial dysfunction.

Endothelial dysfunction is regarded as an early feature of atherosclerotic disease and has been found to be associated with several cardiovascular risk factors. In contrast to the vasodilation induced by serotonin, the vascular response to the other endothelium-dependent vasodilator used, ie, acetylcholine, is normal in HTG patients, corroborating the findings of Chowienczyk et al. At first sight, this contradictory finding may weaken the conclusion that HTG causes endothelial dysfunction. However, previous studies provide strong arguments that in humans serotonin is a more specific tool to investigate endothelium-dependent nitric oxide–mediated vasodilation than is acetylcholine, as argued below.

The present observation that different endothelium-dependent vasodilators cause differential vascular responses is not unique. A similar discrepancy in endothelium-dependent responsiveness was also shown in hypercholesterolemic patients and in patients with type 2 diabetes mellitus (van de Ree et al, unpublished data, 1999), demonstrating the importance of using various vasoactive compounds to investigate the highly complex endothelial system.

Since the first report of Furchgott and Zawadski, acetylcholine has been regarded as the golden standard to study endothelium-dependent nitric oxide–mediated vasodilation. However, from animal studies, there is accumulating evidence that nitric oxide is only partly responsible for acetylcholine-induced vasodilation. It has been demonstrated that acetylcholine can also cause the release of another endothelium-dependent vasodilator, indicated as endothelium-dependent hyperpolarizing factor (EDHF). A recent study in hypercholesterolemic animals demonstrated an impaired nitric oxide–mediated vasodilation; however, the acetylcholine-induced vasodilation was found to be normal because of the increased EDHF response. We speculate that the normal acetylcholine-induced vasodilation in the patients with chronic HTG in the present study may be...
explained by this mechanism, eg, an increased EDHF release.
Very recent evidence suggests that potassium is an EDHF.25

In accordance with these experimental findings, it was previously shown by our group that in the human forearm the vasodilator response to acetylcholine was not influenced by the competitive nitric oxide synthase inhibitor N^G-monomethyl-L-arginine (L-NMMA), whereas serotonin-induced vasodilation was blunted by L-NMMA.26 This finding provides evidence that serotonin is a more specific tool than acetylcholine to investigate endothelium-dependent nitric oxide–mediated vasodilation in humans. On the basis of these experimental and human data, we therefore argue that in HTG, endothelium-dependent nitric oxide–mediated vasodilation is impaired, as measured by the intra-arterial infusion of serotonin. The present finding that infusion of the nitric oxide precursor L-arginine restores serotonin-induced vasodilation in the HTG patients provides further evidence that low nitric oxide availability plays a pivotal role in this impaired responsiveness. The improvement of the acetylcholine-induced vasodilation by L-arginine in the HTG group may be explained by the fact that the acetylcholine response is only partially mediated by the nitric oxide pathway.26

To elucidate the direct effect of triglycerides on endothelial function, a systemic infusion of an artificial triglyceride emulsion (Intralipid) was applied. Previous studies have demonstrated that these artificial lipid particles rapidly acquire apolipoproteins in the circulation and share the same catabolic pathway as endogenous triglyceride-rich lipoproteins.27,28 The finding that acute HTG did not influence the serotonin-induced vasodilation strongly suggests that lipids do not interfere directly with the availability of nitric oxide. This corroborates other studies showing that a prolonged artificial triglyceride load could impair endothelial function indirectly via oxidative mechanisms.7,8,29 The mechanism underlying the paradoxically enhanced response to acetylcholine during the concomitant administration of this artificial triglyceride emulsion is unclear. Previously, a similar paradoxical augmented vasodilator response to intra-arterially infused acetylcholine was observed during the simultaneous infusion of the nitric oxide scavenger methylene blue.26 Evidence was provided that methylene blue enhanced the acetylcholine-induced vasodilation by inactivation of the enzyme acetylcholinesterase.30 Whether a similar mechanism could play a role in the present observation is subject to speculation. Nevertheless, these studies confirm that the vascular effects of acetylcholine are very complex and difficult to interpret.

The present finding, ie, that exogenous administration of the nitric oxide precursor L-arginine improves the endothelium-dependent vasodilation to serotonin in chronic HTG, suggests that low nitric oxide availability may play a pivotal role in this impaired responsiveness. This low nitric oxide availability can be caused by several mechanisms. One possibility is that nitric oxide production is normal but that it is metabolized at a higher rate as a result of circulating lipoproteins, lipolysis products, or oxidation products. Our observation that during acute HTG the endothelium-dependent vasodilation remained unchanged strongly suggests that the lipids do not interfere with the nitric oxide availability directly. The fact that others have reported that a triglyceride load for a longer period of time results in impaired endothelium-dependent vasodilation (a phenomenon that could be prevented by antioxidant therapy with vitamins E and C) indicates that oxidative mechanisms may be involved.7,8,29 An alternative explanation could be that nitric oxide is formed at a lower rate as a result of the decreased availability of L-arginine, the paucity of cofactors, or structural defects in the endothelial cell itself. It is not likely that the endothelial cells are depleted of L-arginine, because the intracellular concentration of L-arginine has shown to be many times higher than necessary for optimal activity of nitric oxide synthase.31 Whether deficiency of the cofactor tetrahydrobiopterin plays a role in HTG, as has been demonstrated in diabetes, smoking, and hypercholesterolemia, remains to be elucidated.32–34 Finally, it is conceivable that high amounts of triglyceride-rich lipoproteins accumulate in endothelial cells, as was recently demonstrated in endothelial cells from atherosclerotic plaques in human coronary arteries.35 Lipid accumulation is associated with structural changes in the cell that may impede its function. Because vasodilatory effects prevail over vasoconstrictive effects in normal endothelial cells, accumulation of triglycerides in endothelial cells may lead to impairment of vasorelaxation.

The fact that the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor atorvastatin could restore endothelial function in HTG patients suggests that treatment with this statin may reduce the risk of cardiovascular disease in this patient group. The mechanism underlying this beneficial effect of atorvastatin remains to be elucidated, although it seems likely that the reduction of the circulating lipid burden by lowering both the triglyceride and cholesterol levels and improving the LDL subclass pattern may play a role. However, there is accumulating evidence that the favorable effects of statins on endothelial function and the prevention of cardiovascular disease are partly independent of their lipid-lowering effects.36,37 Recently, evidence has been provided that nitric oxide availability might be increased by these drugs via upregulation of nitric oxide synthase.38

In conclusion, we have demonstrated that patients with chronic HTG have an impaired endothelium-dependent vasodilation, mediated by the nitric oxide pathway, which is reversed on lipid-lowering therapy by atorvastatin. The observation that induction of an acute artificial HTG does not influence endothelial vasodilation suggests that lipids do not interfere directly with nitric oxide availability.

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References


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