Acute Effect of High-Fat Meal on Endothelial Function in Moderately Dyslipidemid Subjects


Objective—Hypercholesterolemia markedly impairs endothelial function. Whether this is the case for hypertriglyceridemia is less clear, however, and limited evidence exists on the effect of an acute increase in triglyceridemia caused by a high-fat meal.

Methods and Results—In 16 normotensive subjects with an untreated mild hypertriglyceridemia and dyslipidemia and in 7 normal controls, we measured radial artery diameter and blood flow by an echo-tracking device (NIUS02). Data were obtained at baseline, at the release of a 4-minute ischemia of the hand, which causes an increase in arterial diameter dependent on nitric oxide (NO) secretion, and at the release of a 12-minute exclusion of the arm by an arm cuff to obtain a larger increase in arterial diameter mainly of nonendothelial nature. Measurements were performed before and 6 hours after a high-fat meal (680 kcal/m² body surface; 82% lipids). In mild dyslipidemic hypertriglyceridemic subjects, the high-fat meal did not alter baseline blood pressure (beat-to-beat finger measurement), heart rate, radial artery diameter, and blood flow. It also did not alter the increase in blood flow induced by the 4-minute ischemia (+42.7±10.4 and +43.7±10.4 mL/min), whereas it markedly attenuated the concomitant increase in arterial diameter (+0.31±0.06 versus 0.13±0.06 mm; P<0.05). The alteration of the diameter response did not correlate with changes in total cholesterol, but it showed a significant correlation with the increase in serum triglycerides induced by high-fat meal (r=0.49, P<0.05). This attenuation was not seen in control subjects and in subjects in whom measurements were repeated after a 6-hour observation period. It was also not paralleled by an alteration of the endothelially independent response to a 12-minute ischemia whose larger effects on arterial diameter and blood flow were similar before and after the high-fat meal.

Conclusions—Endothelial function is markedly impaired by a high-fat meal that causes an acute hypertriglyceridemia. This impairment is evident in dyslipidemic patients with baseline hypertriglyceridemia but not in normotriglyceridemic controls. (Arterioscler Thromb Vasc Biol. 2005;25:406-410.)

Key Words: blood flow ■ vasodilation ■ endothelium ■ triglyceridemia ■ acute triglyceridemia increase

Several studies have shown that an increased level of serum triglycerides can be an independent risk factor for coronary disease, when occurring alone and when occurring on the background of other alterations in lipid profile.1–4 This has stimulated research on whether triglycerides cause endothelial dysfunction, which starts the cascade of events that lead to the atherosclerosis, ie, the anatomic lesion responsible for coronary heart disease.5–8 Evidence that this is the case is not conclusive, however, because triglycerides were reported both to worsen and to have no measurable effect on endothelial function.9–18 Furthermore, little evidence has been obtained on whether triglycerides affect endothelial function in individuals with more complex, yet common, alterations in lipid profile, despite the evidence that under this circumstance the role of triglycerides as a cardiovascular risk factor may be enhanced.1–4

Our study was aimed at providing further information on this issue by examining the effect of serum triglycerides on endothelial function in subjects with a moderate hypertriglyceridemia and hypercholesterolemia, because this is the most common form of dyslipidemia in the population.19 We measured endothelial function by the magnitude of the flow-mediated increase in radial artery diameter and focused on the effect of a postprandial increase in serum triglycerides for 2 reasons. First, this allowed the effect of a selective modification of the variable undergoing study to be assessed within subjects, ie, in a more precise fashion than that obtainable by comparing subjects with different serum triglycerides levels, which may require adjustment for several concomitant confounding differences. Second, postprandial increases in serum triglycerides have been shown to be predictive of coronary disease more than chronic triglycerides levels.20
Methods

Subjects
We investigated a total of 23 clinically healthy subjects. Sixteen subjects (age, 46.6 ± 2.5 years; means ± SE; 10 males) had a moderate hypertriglyceridemia (>200 mg/dL), whereas the remaining 7 subjects (age, 35.1 ± 2.4 years; males) were normotriglyceridemic volunteers who served as controls. All subjects were normotensive (systolic and diastolic blood pressure <140/90 mm Hg) at 3 sphygmonanometric measurements obtained at a prestudy visit), nonsmokers, and had no drug therapy of any kind, including antioxidant agents. Alcohol consumption was absent or moderate (<1 drink of wine per day) in each individual. Subjects reported a moderate degree of physical activity. They had no clinical sign of alterations in organ structure function, and perfusion caused by atherosclerosis as well as no sign of atherosclerotic disease at an echo color Doppler of femoral arteries, carotid arteries, and abdominal aorta. Thyroid, renal, and hepatic functions were normal at entry. All subjects agreed to participate in the study after explanation of the nature and purpose. The study protocol was approved by the Ethic Committee of the Institution involved.

Measurements
Radial artery diameter was measured by an A-mode ultrasonic echo-tracking device, which recorded the displacement of the radial artery over the cardiac cycle (NIUS 02). The device made use of a transducer of 10 MHz, which was stereotaxically positioned over the radial artery 2 to 4 cm above the wrist, using a gel as a medium. With the subject supine and the arm immobile at the heart level, the radial artery 2 to 4 cm above the wrist, using a gel as a medium. With the subject supine and the arm immobile at the heart level, the radial artery was oriented perpendicularly to the longitudinal axis based on the acoustic Doppler signal, so that its focal zone was located in the center of the artery, and the backscattered echoes from both the anterior and the posterior walls could be visualized and acquired at 50 Hz. The device resolution allowed the identification of diameter changes of 0.0025 mm during blood pressure changes from diastolic to systole. The device also made use of a photoplethysmographic system (Finapres; Ohmeda, Englewood, Col), which allowed blood pressure to be recorded noninvasively from a finger ipsilateral to the radial artery examined with an accuracy similar to intra-arterial radial artery pressure and a resolution of 2 mm Hg. Heart rate was calculated as the reciprocal of the interval between 2 successive beats.

Blood flow velocity was measured at the same site of the diameter measurement by a 8-MHz probe positioned with an angle of 40 to 60 degrees from the principal axis of the artery. Blood flow was calculated as the product of flow velocity and arterial diameter. Blood flow velocity was continuously measured for 15 minutes (baseline); (6) in 8 hypertriglyceridemic and 4 control subjects, the cuff placed on the wrist was inflated at suprasystolic pressure for 4 minutes, with the aforementioned hemodynamic variables being recorded over 4 minutes after the release of inflation; (7) after a 10-minute interval, radial artery diameter, blood pressure, and blood flow velocity were continuously measured for 15 minutes (baseline); (8) in the remaining subjects, the 12-minute arm ischemia preceded the 4-minute hand ischemia. In all subjects, the protocol was repeated on the same day, 6 hours after they had consumed an OFL consisting of 680 kcal/m2 of body surface with 83% fat, 5% proteins, 12% carbohydrates, and 600 mg cholesterol over a 20-minute time interval. The OFL is a modification of the test proposed by Patsch. Blood samples were collected in tests tubes containing NaEDTA (0.1 mg/mL) before and at 6 hours from OFL using a vein contralateral to the arm where radial artery measurements were made. During the 6-hour interval, no food or drinks were permitted, except water. In 6 hypertriglyceridemic subjects, all hemodynamic measurements were repeated also on a different day, before and after a 6-hour observation period. Data analysis in each subject’s baseline values for arterial diameter and blood flow were calculated by averaging 5 30-second measurements obtained during the initial 15-minute period. The blood flow and radial artery diameter responses to either the 4-minute or the 12-minute ischemia were assessed as the peak value during the 60 seconds and the 180 seconds that followed the cuff pressure release, respectively. Acquisitions were all made by a single investigator, whereas data analysis was performed by investigators unaware of the protocol. In our laboratory, the intra-observer coefficient of variation of radial artery diameter values (calculated from 2 sets of values obtained in standardized conditions) is 2.5% for baseline measurements, 3.5% for measurements performed after 4-minute ischemia, and 1.9% after 12-minute ischemia. The corresponding values for radial artery blood flow are 8.0%, 9.0%, and 7.0%. The statistical significance of the differences in mean values was assessed by 2-way analysis of variance. The 2-tailed t test for paired observations was used to locate differences. Linear correlation was also sought between changes in lipid variables and endothelial-dependent response induced by OFL. P < 0.05 was taken as the level of statistical significance. Throughout the text, the symbol “±” refers to the standard error of the mean.

Protocol
The study was performed in a temperature-controlled (21°C) laboratory. The protocol was as follows: (1) subjects were asked to withdraw from any alcohol consumption, as well as any excessive food intake, physical activity, and other departure from usual lifestyle in the 3 days before the study; (2) they were brought to the laboratory in the morning and put in the supine position; (3) blood was withdrawn from an antecubital vein for measuring serum triglycerides, total cholesterol, and high-density lipoprotein cholesterol; (4) the radial artery echo-tracking device, the blood pressure measuring devices, and the wrist and arm cuffs were ready; (5) after a 10-minute interval, radial artery diameter, blood pressure, and blood flow velocity were continuously measured for 15 minutes (baseline); (6) in 8 hypertriglyceridemic and 4 control subjects, the cuff placed on the wrist was inflated at suprasystolic pressure for 4 minutes, with the aforementioned hemodynamic variables being recorded over 4 minutes after the release of inflation; (7) after a 10-minute interval, the cuff placed around the arm was inflated at suprasystolic pressure for 12 minutes, with the aforementioned variables being recorded over 4 minutes after the release of inflation; and (8) in the remaining subjects, the 12-minute arm ischemia preceded the 4-minute hand ischemia. In all subjects, the protocol was repeated on the same day, 6 hours after they had consumed an OFL consisting of 680 kcal/m2 of body surface with 83% fat, 5% proteins, 12% carbohydrates, and 600 mg cholesterol over a 20-minute time interval. The OFL is a modification of the test proposed by Patsch. Blood samples were collected in tests tubes containing NaEDTA (0.1 mg/mL) before and at 6 hours from OFL using a vein contralateral to the arm where radial artery measurements were made. During the 6-hour interval, no food or drinks were permitted, except water. In 6 hypertriglyceridemic subjects, all hemodynamic measurements were repeated also on a different day, before and after a 6-hour observation period. Data analysis in each subject’s baseline values for arterial diameter and blood flow were calculated by averaging 5 30-second measurements obtained during the initial 15-minute period. The blood flow and radial artery diameter responses to either the 4-minute or the 12-minute ischemia were assessed as the peak value during the 60 seconds and the 180 seconds that followed the cuff pressure release, respectively. Acquisitions were all made by a single investigator, whereas data analysis was performed by investigators unaware of the protocol. In our laboratory, the intra-observer coefficient of variation of radial artery diameter values (calculated from 2 sets of values obtained in standardized conditions) is 2.5% for baseline measurements, 3.5% for measurements performed after 4-minute ischemia, and 1.9% after 12-minute ischemia. The corresponding values for radial artery blood flow are 8.0%, 9.0%, and 7.0%. The statistical significance of the differences in mean values was assessed by 2-way analysis of variance. The 2-tailed t test for paired observations was used to locate differences. Linear correlation was also sought between changes in lipid variables and endothelial-dependent response induced by OFL. P < 0.05 was taken as the level of statistical significance. Throughout the text, the symbol “±” refers to the standard error of the mean.

Results
Table 1 shows that at baseline, subjects recruited for their abnormal lipid profile had significantly greater serum triglycerides and cholesterol than controls. Compared with controls, hypertriglyceridemic subjects had somewhat higher blood pressure and radial artery diameter and somewhat lower heart rate and radial artery blood flow values, with no difference, however, being statistically significant. In the control group, OFL caused no significant change in blood pressure, heart rate, radial artery diameter, and flow, as well as no change in lipid profile components except for an increase in serum triglycerides. This was the case also in hypertriglyceridemic subjects in whom the increase in serum triglycerides was more pronounced. As shown in Figure 1, before OFL the 4-minute ischemia caused a clear-cut significant increase in radial artery blood flow (greater in controls than in hypertriglyceridemic subjects) with a similarly marked significant
increase in radial artery diameter in the 2 groups. After OFL, the increase in flow and diameter remained unaltered in controls, whereas in hypertriglyceridemic subjects the increase in flow was unchanged but the concomitant increase in diameter was significantly reduced. The reduction was marked to make the change from the pre-ischemic value no more significant. In the 6 subjects restudied on 2 different days, the responses to 4-minute ischemia were similar before and after the 6-hour observation period, ie, the increase in flow were 34.0 ± 9.2 mL/min, and the increase in arterial diameter were 0.42 ± 0.07 and 0.48 ± 0.11 mm. The 12-minute arm ischemia increased blood flow and arterial diameter more than the 4-minute hand ischemia, with no difference before and after OFL in all groups (Table 2).

**Discussion**

In our subjects, we measured endothelial function by the increase in radial artery diameter induced by release of a 4-minute hand ischemia because previous studies have shown this increase to be abolished by administration of L-NAME and thus to depend on a flow-mediated and shear-stress-mediated secretion of NO from endothelial cells. The results show that in the fasting condition, the 4-minute ischemia caused a clear-cut flow-mediated increase in radial artery diameter in control normotriglyceridemic subjects and in hypertriglyceridemic subjects. They also show, however, that an OFL had little effect on the radial artery response in controls but it markedly altered the flow-mediated increase in radial artery diameter in hypertriglyceridemic subjects. They finally show that in both groups, OFL did not have any effect on the NO-independent larger increase in radial artery blood flow and diameter induced by a much more prolonged ischemia. Thus, an OFL does not affect NO function in normal individuals while markedly impairing the ability of NO secretion to modulate vasomotor tone in subjects with a chronic increase in serum triglycerides. This appears to reflect a specific endothelial effect, because vascular reactivity to substances other than NO that were released by ischemia was not affected by OFL in hypertriglyceridemic subjects and in normotriglyceridemic controls.

Several other results of our study deserve a comment. In controls and in hypertriglyceridemic subjects, OFL did not modify the arterial diameter values before ischemia, which allows us to conclude that the different effect of OFL on the response to short-term ischemia seen in the 2 groups did not depend on alterations in baseline values. We found that in hypertriglyceridemic subjects, the flow-mediated changes in radial artery diameter induced by short- and long-lasting ischemias were unaffected by an observation period of a duration similar to that used for collecting post-OFL data. Thus, an OFL does not affect NO function in normal individuals while markedly impairing the ability of NO secretion to modulate vasomotor tone in subjects with a chronic increase in serum triglycerides. This appears to reflect a specific endothelial effect, because vascular reactivity to substances other than NO that were released by ischemia was not affected by OFL in hypertriglyceridemic subjects and in normotriglyceridemic controls.**

![Figure 1. Changes in radial artery blood flow and diameter values induced by release from 4-minute hand ischemia performed before and 6 hours after oral fat load (OFL) in 7 controls and in 16 hypertriglyceridemic subjects. Mean (±SE) changes are shown. *P < 0.05 versus baseline. P<0.05 versus before OFL.](image)

**TABLE 1. Hemodynamic and Serum Lipid Values (means ± SE) Before and 6 Hours After OFL in 16 Hypertriglyceridemic Subjects and 7 Healthy Controls**

<table>
<thead>
<tr>
<th></th>
<th>Controls Before OFL</th>
<th>Controls After OFL</th>
<th>Hypertriglyceridemic Subjects Before OFL</th>
<th>Hypertriglyceridemic Subjects After OFL</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>120.7 ± 5.2</td>
<td>118.3 ± 4.1</td>
<td>132.6 ± 3.9</td>
<td>124.5 ± 4.2</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>72.2 ± 3.8</td>
<td>74.3 ± 4.0</td>
<td>81.0 ± 2.6</td>
<td>74.1 ± 2.8</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>78.0 ± 3.0</td>
<td>76.0 ± 4.0</td>
<td>66.6 ± 2.7</td>
<td>67.2 ± 2.7</td>
</tr>
<tr>
<td>RA blood flow, mL/sec</td>
<td>45.1 ± 20.3</td>
<td>52.3 ± 19.3</td>
<td>41.7 ± 17.4</td>
<td>39.3 ± 4.5</td>
</tr>
<tr>
<td>RA diameter, mm</td>
<td>2.1 ± 0.1</td>
<td>2.1 ± 0.1</td>
<td>2.5 ± 0.1</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>170.5 ± 10.2</td>
<td>178.0 ± 15.0</td>
<td>244.6 ± 9.9†</td>
<td>241.3 ± 10.9</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>38.8 ± 4.0</td>
<td>39.0 ± 3.9</td>
<td>40.3 ± 4.3</td>
<td>40.5 ± 4.4</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>130.0 ± 2.1</td>
<td>132.4 ± 2.0</td>
<td>163.4 ± 13.6†</td>
<td>165.5 ± 13.0</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>57.6 ± 7.0</td>
<td>84.1 ± 12.0*</td>
<td>250.1 ± 33.7†</td>
<td>469.7 ± 48.0**</td>
</tr>
</tbody>
</table>

*P < 0.05.
**P < 0.01 vs before OFL.
†P < 0.01 vs controls.

bp indicates beats per minute; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OFL, oral fat load; RA, radial artery; SBP, systolic blood pressure.
arterial response to 4-minute ischemia after OFL showed no correlation with the OFL-induced change in total, low-density lipoprotein, or high-density lipoprotein cholesterol (r never >0.2) but a significant correlation with the OFL-induced increase in serum triglycerides (Figure 2).

Although there is absence of data on remnant cholesterol and particles, participation of the cholesterol fraction in the acute impairment of endothelial function cannot be totally excluded. This favors a major triglycerides role.

The inability of OFL to adversely modify endothelial function in normotriglyceridemic subjects is in line with the results of some, but not all, previous studies.\(^6\) \(^7\) \(^8\) \(^9\) \(^10\) It is clear from our data, however, that regardless of whether an effect is there in normotriglyceridemia, the damaging OFL-related effect on endothelium is exacerbated by the existence of a baseline increase in this lipid component. We can speculate that this originates from the fact that postprandial absolute serum triglycerides are much lower in normotriglyceridemic individuals because of the lower baseline values and the smaller increase after OFL (47% versus 88%), which implies that serum triglycerides may have a threshold value below which endothelial function is not affected.

Our results have pathophysiological implications because endothelial dysfunction is the first step in the chain of arterial wall modifications that allow an atherosclerotic lesion to start and progress.\(^5\) \(^6\) \(^7\) \(^8\) \(^9\) \(^10\) \(^11\) \(^12\) They may thus provide an explanation for the epidemiological finding that transient increases in serum triglycerides increase the risk of coronary disease,\(^20\) a disease caused by coronary artery atherosclerosis. It remains to be seen whether acute hypertriglyceridemia affects just the ability of endothelial cells to increase their NO secretion (the endothelial function “reserve”) or if it extends to the continuous secretion of this substance under baseline conditions; whether a similar adverse effect occurs in individuals with more severe and/or different types of dyslipidemia than just moderate hypertriglyceridemia and hypercholesterolemia; and whether data collected in an artery devoid of atherosclerotic lesions reflect the effect of acute hypertriglyceridemia on endothelial function of coronary, carotid, and other arteries whose atherosclerotic damage is directly responsible for the appearance of cardiovascular morbidity and fatal events. It should be emphasized, however, that the observation that hypertriglyceridemia causes endothelial dysfunction in the radial artery has a special interest, because it suggests the effect to be an early one and, thus, it can precede and cause the later anatomic lesions.

### References

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C. Giannattasio, A. Zoppo, G. Gentile, M. Failla, A. Capra, F.M. Maggi, A. Catapano and G. Mancia

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