

The Effect of an Acute Fat Load on Endothelial Function after Different Dietary Regimens in Young Healthy Volunteers

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Summary

Attention has recently been focused on endothelial function after a single high-fat meal, i.e. on the anticipated direct atherogenic effect of triglyceride-rich lipoproteins. Our study was designed to investigate the effect of a low-fat diet given for four weeks followed by a high-fat diet for another four weeks. At the end of each dietary period, a non-invasive ultrasound investigation of endothelial function of the brachial artery was performed along with laboratory tests. Endothelial function was measured immediately before the dietary load and after three and six hours in 11 healthy volunteers. The results were expressed as percentage of the changes in artery diameter at rest and during hyperemia; the data were processed using computer technology. When compared to the low-fat regimen, the total cholesterol content rose after the high-fat diet from 4.28 mmol/l to 5.15 mmol/l ($p < 0.05$) in the whole group of volunteers. There was no difference between both dietary regimens in baseline triglycerides. The brachial artery dilatation under basal conditions was 5.26 ± 2.88 mm after the high-fat diet compared with the value of 3.13 ± 3.01 mm ($p < 0.05$) after the low-fat diet. When measured individually endothelial function in the whole group of volunteers in the course of the day, the degree of arterial dilatation after one month on low-fat diet was 3.13 ± 3.0 %, 3.88 ± 2.5 % and 5.23 ± 3.3 % at single measurement. When comparing arterial dilatation at two closest measurements, a non-significant trend, $p > 0.05$ was seen in either case. The following values were obtained after one month on the high-fat diet: 5.26 ± 2.9 %, 4.47 ± 1.7 %, and 6.2 ± 3.6 %; again showing a non-significant trend of $p > 0.05$. In this study, a single high-fat meal at the different dietary regimen did not significantly influence the vasoreactivity of the brachial artery in young volunteers.

Key words

Postprandial lipemia • Hypertriglyceridemia • Endothelial dysfunction • Diet

Introduction

The endothelium is the largest endocrine organ weighing about 1.5 kg. It forms the inner lining of all

vessels in the human body. One of its basic physiological functions is to ensure an optimal vessel diameter, to maintain the equilibrium of the coagulation processes, to mediate inflammatory and immunological responses, and

to ensure the integrity and structure of the vessel wall. Endothelial function impairment is a basic factor implicated in the origin and development of blood vessel diseases (Vogel *et al.* 1998). Endothelial dysfunction can be considered the first, functionally significant stage of atherosclerosis. It is used to indicate the impairment of endothelial-dependent vasodilatation; however, it probably includes conditions leading to endothelial activation where abnormal interactions with leukocytes, blood platelets, and regulatory substances occur (Anderson 1999). The factors most often implicated in the development of impaired endothelial function include hyperlipoproteinemia, arterial hypertension, smoking, non-insulin dependent diabetes mellitus, hyperhomocysteinemia, endothelial dysfunction caused by inflammation, immunocomplexes, or medication (Šejda 2000).

Triglyceride-rich lipoproteins are now recognized as a risk factor for the development of ischemic heart disease (IHD), associated primarily with low HDL-cholesterol levels, the presence of small dense LDL particles, hyperinsulinemia, and insulin resistance (Gotto *et al.* 1998). Triglyceride-rich lipoproteins have been shown to be an independent risk factor for the development of IHD in a specific patient group (Gotto and Phil 1998). A number of publications deal with hypotheses concerning the atherogenic effect of triglyceride-rich lipoproteins resulting from a single high-fat meal, or after the intravenous application of "Intralipid". In this case, the mechanism of the atherogenic effect is based on inducing endothelial dysfunction as an early manifestation of atherosclerosis. The reactive hyperemia affecting the vasoreactivity e.g. of the brachial artery, is a sensitive, nitric oxide (NO)-dependent index of endothelial function correlating with coronary arterial vasoreactivity after acetylcholine administration (Anderson *et al.* 1995). Recent studies have demonstrated comparable impairment of the endothelial function of coronary and brachial arteries associated with risk factors of atherosclerosis (Celermajer *et al.* 1994).

The aim of this study was to determine the vasoreactivity of the brachial artery after a high-fat (HF) load using two different dietary regimens, each of them used for a one-month period. A low-fat (LF) diet was given to healthy volunteers for four weeks, followed by HF diet for the next four weeks. To determine whether the employed dietary regimen and a single dietary load would cause endothelial function impairment of the brachial artery, a non-invasive, high-resolution ultrasound

method was used to assess the extent of arterial dilatation in the course of reactive hyperemia.

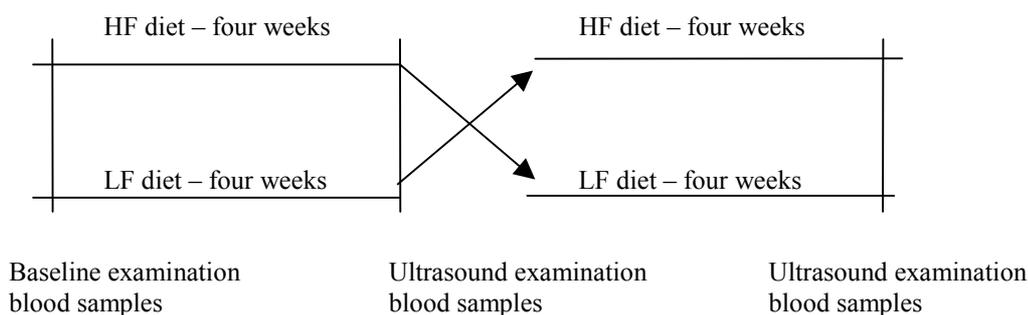
Table 1. Structure of low-fat (LF) and high-fat (HF) diet

	LF diet	HF diet
<i>Energy</i>		
<i>kJ/70 kg of weight</i>	10 525	10 525
<i>Fats</i>		
<i>g/70 kg of weight</i>	70.2	120.1
<i>Saccharides</i>		
<i>g/70 kg of weight</i>	402.9	279.5
<i>Proteins</i>		
<i>g/70 kg of weight</i>	84.1	84.1
<i>Fats</i>		
<i>energy portion in %</i>	26	44.5
<i>Cholesterol</i>		
<i>mg/70 kg of weight</i>	204	611

Methods

The experimental protocol

The volunteers were given the LF diet for four weeks and the HF diet for the ensuing four weeks. The composition of the diets was close to that designed for preventing cardiovascular diseases (LF diet), and to that typical for the Czech population (HF diet), see Table 1. The order of the diets was randomized, the study was run in a "cross-over" manner (for the schedule see Fig. 1). The decision to use both diets for four weeks each was made on the basis of a pilot study demonstrating that the diets were isocaloric, that they were associated with no weight gain after 6 weeks, and that cholesterolemia increased after 4 weeks compared with the baseline. Nevertheless, its level no longer tended to rise does not change further (Kovář *et al.* 1999, Kovář and Poledne 2000). At the end of each dietary period, ultrasound measurements of brachial artery vasoreactivity were carried out at 7:00 h, after a 12-hour fast. Half an hour after the ultrasound examination, the volunteers received a dietary load (cream cake, doughnut, and cocoa) containing 57.5 kJ /Kg (44.8 % fats, 46.8 % saccharides, 25.1% proteins). Three and six hours after the dietary load, the ultrasound investigation was repeated with blood samples obtained at an interval of 90 min over a 9-hour period. The volunteers were allowed to drink only water or coffee and sugar-free beverages during the investigation. The volunteers were asked to sign their informed consent before joining the study.

Fig. 1. Study schedule*Characteristics of volunteers*

A total of 11 healthy volunteers (six men and five women) 24 ± 4.6 years old with BMI 22.8 ± 1.7 kg/m², mean systolic and diastolic blood pressure 112 ± 6.2 and 74 ± 8.1 mm Hg, respectively, took part in the study. Their mean total cholesterol level was 4.6 ± 0.86 mmol/l, triglycerides 1.4 ± 0.85 mmol/l, HDL-cholesterol 1.3 ± 0.26 mmol/l, and glycemia 5.15 ± 0.45 mmol/l. One of the volunteers was a cigarette smoker (7 cigarettes per day), three women used hormonal contraception (low-dose contraception, "micropills"). The apolipoprotein (apo) genotype E 3/3 was identified in eight cases, while the apo E 3/4 form was found in the other cases (as determined using PCR). The women joined the study at the same period of their menstrual cycle, between days 5 and 12. Body weight was monitored throughout the study so that the energy intake could be adjusted accordingly in the case of body weight changes.

Ultrasonography technique and evaluation of hyperemic phase

Brachial artery vasoreactivity was measured non-invasively using the method developed by Celermajer *et al.* (1992). Endothelial flow-dependent brachial artery dilatation was determined using an Accuson 128 XP/4 ultrasound system (Mountain View, California, USA) with a linear-array 7 MHz transducer. In brief, the brachial artery diameter was measured on B-mode ultrasound images. Continuous videorecordings were obtained on VHS Sony-V PRO-X videocassettes throughout the investigation. The investigations were carried out with the patient in the supine position, in a quiet dark room at room temperature. After a 10-min rest, blood pressure and heart rate were measured using an automatic oscillometer (Boso Oscillomat, Bosch + Sohn, GmbH, Jungingen, Germany). The brachial artery was located about 5 cm above the antecubital fossa of the

right arm and was identified by means of pulse Doppler. After starting the video recording, two reference points were assigned making it possible to keep the transducer in the same position during the entire investigation. On completion of the recording at rest, arterial occlusion was applied on the right forearm by means of a cuff attached to a conventional mercury sphygmomanometer inflated to a pressure of 50 mm Hg above systolic pressure. After a 4-min arterial occlusion, the cuff was deflated and, a video recording was obtained for an additional 2 min in the subsequent hyperemic phase. Image analysis was performed off-line using an Autocont Pentium PC (Autocont, Prague, Czech Republic) with "Image Pro Plus" software (Media Cybernetics, Silver Springs, Maryland, USA). The required portion of the recording was transferred from the videocassette to the PC monitor where artery diameter was repeatedly measured in separated sequences by means of calipers. The artery diameter measurement was always made at the end of the diastole (representing maximum dilatation) at 5-second intervals, six times in the resting phase and six times within 30-60 seconds after cuff deflation. All material measurements and computer-assisted analyses were performed by the same physician without optical control. In a separate study (Pit'ha *et al.* 2002), coefficient of variation (3.21 %) was calculated in 10 individuals, repeatedly evaluated at seven-day intervals. The change of the arterial diameter in the hyperemic phase was expressed as percentage.

Lipid determination

A venous catheter was introduced into the left forearm at the end of either dietary regimen before the LF or HF diet, and baseline blood samplings were withdrawn. The samples were used to determine total cholesterol, triglycerides, and HDL-cholesterol by enzymatic methods (Boehringer, Mannheim, Germany).

LDL-cholesterol was calculated using Friedewald's formula. Blood sampling was performed at 90-min intervals for nine hours every day. Postprandial hypertriglyceridemia was assessed as part of postprandial lipidemia studies.

Statistical methods

The results were expressed as means±SD. Statistical testing of the differences between the resting values and those determined during reactive hyperemia was performed using Student's paired t-test.

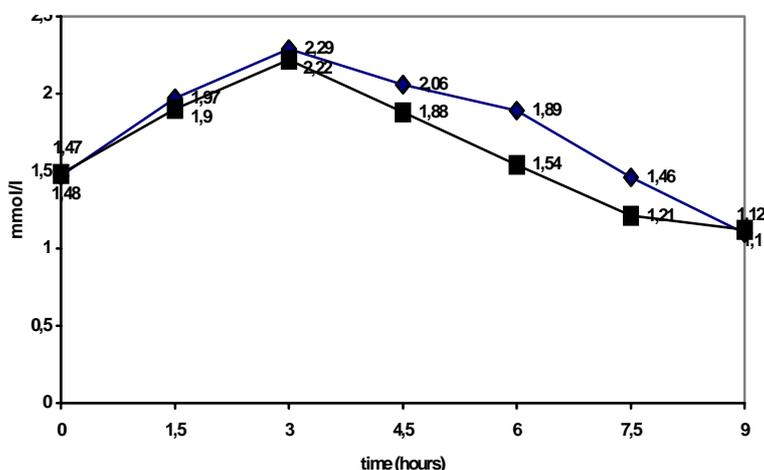


Fig. 2. Values of serum triglycerides in the course of the day on dietary load after HF and LF regime.

◆ HF - high-fat diet, ■ LF - low-fat diet

Table 2. The lipid parameters after different dietary regimens

	LF diet	HF diet
Total cholesterol	4.28±1.28	5.16±1.3*
HDL cholesterol	1.21±0.21	1.53±0.37
LDL cholesterol	2.41±0.88	2.97±1.05•
Triglyceride	1.46±1.52	1.52±0.67

LF low-fat; HF high-fat diet, * $p < 0.05$; • $p = 0.05$, in mmol/l±S.D.

Results

The mean values of individual lipid parameters obtained after different dietary regimes are listed in Table 2. Cholesterol levels were after HF diet higher by 20.5% compared with the LF diet in all subjects; no significant differences in triglyceride or HDL-cholesterol levels were observed at baseline blood sampling after either dietary regimen. After the dietary load, plasma triglyceride concentration peaked within 3 to 4 hours (56% to HF, 50% to LF), returning to baseline within 6 to 7 hours (Fig. 2).

The brachial artery diameters at rest and during hyperemia in the whole group of volunteers at individual

points of time (i.e. before dietary load administration and 3 and 6 hours after the load) are shown in Table 3. The brachial artery dilatation in the hyperemic phase (expressed as percentage) is also shown in Table 3. Compared with the resting phase, a statistically significant artery dilatation in the hyperemic phase was always found at single measurements.

Furthermore, the degree of arterial dilatation at baseline was compared with that determined 3 h after the dietary load and between the dilatation, as determined 3 h and 6 h after the load. The test was performed separately for both dietary regimens (see Tab. 3). In the course of the day, no statistically significant difference in arterial dilatation in the hyperemic phase was observed on either dietary regime. Similar results were obtained in a subgroup of women showing no significant difference in the degree of arterial dilatation during the day with both dietary regimens. In a subgroup of men, when comparing baseline dilatation with that three hours after the dietary load, a $p = 0.06$ was calculated (i.e. at the limit of statistical significance); other results are similar to those determined for the entire group.

When comparing total cholesterolemia at baseline blood samples, there was a significant increase from 4.28±1.08 mmol/l after LF to 5.16±1.3 mmol/l after HF ($p < 0.05$). On the other hand, arterial dilatation at basal measurements was 5.26±2.88 after HF in contrast to

LF with a value of 3.13 ± 3.01 ($p < 0.05$). The results obtained when comparing the other two measurements, made after the LF and HF diet at the same time, were not significantly different.

Finally, there was always significant brachial artery dilatation in the hyperemic phase compared with the resting phase in each individual examination.

However, no differences in vasoreactivity were noted during the examination when comparing endothelial function at basal measurement with that obtained 3 h after the dietary load, or when comparing the values obtained 3 h and 6 h after the dietary load. The vasoreactivity was not influenced by a single HF load delivered at different dietary regimens.

Table 3.

The diameters of brachial artery is in rest and hyperemic phase (mm±S.D.), changes of brachial artery diameter and comparison of two closest measurements before and after high fat load (%±SD) in the course of the day after LF and HF diet the whole group (n = 11)

	7:00 h fasting	Comparison of two closest changes of diameter (%)	11:00 h 3 h after high fat load	Comparison of two closest changes of diameter (%)	14:00 h 6 h after high fat load
LF diet					
<i>Resting phase (mm)</i>	3.99±0.47		3.93±0.47		4.01±0.55
<i>Hyperemic phase(mm)</i>	4.11±0.42		4.08±0.47		4.24±0.54
<i>Change of diameter (%)</i>	3.13±3.01*	0.74±2.98 NS	3.88±2.50**	1.36±2.46 NS	5.23±3.32**
HF diet					
<i>Resting phase(mm)</i>	3.97±0.52		4.09±0.49		4.05±0.49
<i>Hyperemic phase(mm)</i>	4.18±0.55		4.27±0.55		4.30±0.55
<i>Change of diameter(%)</i>	5.26±2.9**	0.78±2.65 NS	4.47±1.70**	1.67±3.69 NS	6.16±3.64**

LF low-fat, HF high-fat diet, * $p < 0.01$, ** $p < 0.001$, NS statistically nonsignificant

Discussion

This study designed to assess the influence of a HF load on brachial artery vasoreactivity at different dietary regimens failed to demonstrate any effect. The effect of triglyceride-rich lipoproteins on endothelial function, as determined on the brachial artery, has been described as being controversial. Significantly decreased endothelial function of the brachial artery was shown in studies by Vogel *et al.* (1997) and Lundman *et al.* (1997) where a single dietary HF load had been used or where intravenous "Intralipid" had been applied. On the contrary, Djousse *et al.* (1999) and Raitakari *et al.* (2000) found no effect in this respect. In another study (Schnell *et al.* 1999) no significantly impaired dilatation of the brachial artery in the hyperemic phase was found in patients with a moderate increase in triglycerides or LDL-cholesterol levels with no other risk factors of atherosclerosis. However, a single dietary load was not used in this report. In another study (de Man *et al.* 2000)

patients with chronic hypertriglyceridemia had an impaired endothelium-dependent vasodilatation, but acute hypertriglyceridemia did not influence endothelial vaso dilatation. When measuring the endothelial function of the popliteal artery (Spáčil *et al.* 1999), significant arterial dilatation in the hyperemic phase was demonstrated in healthy persons; on the other hand, significantly reduced dilatation was demonstrated in patients with hyperlipidemia or ischemic heart disease (IHD).

Hypertriglyceridemia has recently been re-established as a risk for developing premature atherosclerosis. An important factor in the relation of triglycerides and IHD is the heterogeneity of lipoprotein transporting triglycerides (triglyceride-rich lipoproteins). These particles formed immediately after a dietary load (chylomicrons) are not associated with the risk for the development of IHD and their extreme values are associated with the possibility of acute pancreatitis. On the contrary, the chylomicron remnant particles ensuing

from them, and IDL-cholesterol as a remainder of VLDL-cholesterol-ensuing particles are considered highly atherogenic (Brewer 1999). In some studies, the degree of postprandial lipemia has been associated with insulin resistance, hyperinsulinemia, and it has also been indicated as a risk factor for the development of IHD independent of whether or not LDL-cholesterol increases (Gotto and Phil 1998).

Isolated hypertriglyceridemia was identified as an independent risk factor in women aged 50 to 69 years in the Framingham study (Castelli 1992), in patients with non-insulin dependent diabetes mellitus in the Paris Prospective study (Fontbonn *et al.* 1989), and in men in the Copenhagen study with medium and higher degree hypertriglyceridemia determined as an independent predictor for the development of IHD (Jeppessen *et al.* 1998). This conclusion was confirmed in a meta-analysis of 17 prospective population-based studies (Hokanson and Austin 1996). Hypertriglyceridemia is classified as a metabolic condition associated with an increased risk for the development of atherosclerosis. The above conditions include postprandial lipemia, insulin resistance, hyperinsulinemia, small dense LDL particles, increased LDL particles oxidability, and central obesity (Gotto and Phil 1998, Brewer 1999).

The number of volunteers doubtlessly represents a limitation to this study; however, it did not differ from that reported in the above studies. An advantage of this study was the possibility of exact measurement of the brachial artery diameter using a computer. The slight difference in triglyceridemia in basal blood sampling after both dietary regimens can be due to the isocaloric diet characteristics (Table 1). The reason for comparing two nearby measurements was whether the current changes in triglyceridemia would result in a change in endothelial function, which was to be related to the nature of the dietary load and, subsequently, monitoring the plasma triglyceride concentration in the course of the day (Fig. 2)

After a four-week HF regimen, brachial artery dilatation under basal conditions was significantly higher, the same as the increase in total cholesterolemia, compared with the LF regimen. It should be emphasized again that young, healthy volunteers took part in the study, and there was an intraindividual difference in the results obtained at individual measurements in one-month intervals. There is no doubt that numerous factors act in synergy to affect endothelial function (Celermajer *et al.* 1992), and there is variability between individual examinations on different days (Anderson 1999). Schnell *et al.* (1999) did not demonstrate impaired brachial artery dilatation in patients with moderately increased LDL-cholesterol but without other risk factors of atherosclerosis compared with individuals with normal LDL-cholesterol levels.

The reason for the different findings obtained when monitoring the effect of a single dietary load on brachial artery vasoreactivity in the above studies remains unclear. The group of volunteers, the dietary load, and postprandial triglyceridemia in these studies are comparable. Further study of endothelial function and the effect of individual lipid fractions on the development of endothelial dysfunction as the first functionally significant stage of atherosclerosis should be carried out. It can be concluded that a HF load applied in a single dose does not significantly influence brachial artery vasoreactivity in young, healthy volunteers after four weeks of low and high-fat diet regimes.

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Reprint requests

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