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High-fat meal impairs vascular compliance in a subgroup of young healthy subjects

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Abstract

Postprandial hypertriglyceridemia impairs endothelial function and may possibly worsen vascular compliance by increasing oxidative stress. Large (C_1) and small (C_2) artery compliance, glucose, insulin, and triglycerides (TGs) were measured hourly for 6 hours in 18 young healthy volunteers after a low-fat meal and a high-fat meal, with and without antioxidant vitamins. C_1 and C_2 declined significantly for 6 hours after fat ingestion in 8 subjects ("fat reactors") and increased in 10 ("nonreactors"). Fat reactors had higher fasting and peak serum TGs after fat loading and increased baseline glucose and insulin levels and homeostasis model assessment of insulin resistance ($HOMA_{IR}$). Fasting insulin correlated with C_1 and C_2 only in fat reactors. After fat intake, plasma nitric oxide metabolites decreased more in fat reactors than in nonreactors (17.0% ± 5.1% vs 4.8% ± 2.1%; $P < .05$). In fat reactors, pretreatment with antioxidant vitamins before the high-fat meal blunted the fall in C_1 but not in C_2. Compliance was unchanged after the low-fat meal. Normal weight young subjects with an insulin resistance phenotype show significantly decreased vascular compliance, increased postprandial TG peaks, and markedly reduced plasma nitric oxide metabolites after a high-fat meal.

1. Introduction

The search to understand the pathological mechanisms of cardiovascular disease (CVD) has currently focused on the vascular endothelium, a repository of proinflammatory substances [1] and modulators of vasomotor tone such as nitric oxide (NO) and reactive oxygen species [2-4]. Increased oxidative stress and alterations in endothelial function, which contribute to the development of atherosclerosis, hypertension, and diabetic vasculopathy [5], are independent predictors of cardiovascular events [6].

Insulin resistance (IR) is associated with increased risk for type 2 diabetes and CVD [7]. Although obesity and IR are clearly associated, obese individuals are not always insulin resistant, and conversely, a significant proportion of insulin-resistant individuals are of normal weight [8]. Insulin resistance may precede the onset of obesity and is related both to genetic factors and to a more sedentary lifestyle and increased dietary fat intake. Triglyceride (TG)-rich lipoproteins induced by high-fat diets have been shown to be atherogenic and are increasingly considered an independent CVD risk factor [9,10]. A single high-fat meal can induce endothelial activation [1] and impair flow-mediated vasoactivity in healthy subjects [11,12] and in experimental animals [13,14], possibly resulting from TG-induced oxidative stress [4]. In healthy subjects and diabetic patients, the combination of postprandial hypertriglyceridemia and hyperglycemia may have an additive effect in producing oxidative stress [15], evaluated indirectly as increased plasma nitrotyrosine [16]. Moreover, in lean insulin-sensitive subjects, free fatty acid elevation (that happens subsequent to a high-fat load) was shown to impair both the shear stress–induced NO production and insulin-mediated vasodilation, but with different time courses and thus probably via different signaling pathways [17].

The atheroprotective effect of antioxidant vitamins is controversial. In the Heart Outcomes Prevention Evaluation (HOPE) trial, long-term antioxidant therapy failed to improve

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cardiovascular outcomes in diabetes [18]. In contrast, a single dose of antioxidant vitamins can reduce the effect of a high-fat meal in stimulating the release of inflammatory markers (tumor necrosis factor α, interleukin 6, intercellular adhesion molecule 1, vascular cell adhesion molecule 1 [1]) in reducing the reduction in flow-mediated vasodilation [11].

This study was conducted to investigate the effects of an oral fat load on vascular compliance in young healthy subjects who were free of confounders that might potentially affect compliance such as drug therapies, smoking, or chronic disease. We evaluated hourly changes in large (C_1) and small artery compliance (C_2) by pulse contour analysis [19]. This is a reproducible noninvasive method used in assessing the presence of preclinical vascular disease [20-23]. In addition, we measured changes in blood glucose, insulin, and TG after a high-fat meal, an isoenergetic fat-free carbohydrate meal, and a high-fat meal preceded by the antioxidant vitamins C and E.

2. Research design and methods

2.1. Subjects

Eighteen physically active subjects (7 men and 11 women, ages 18-24 years; mean age, 21.0 ± 0.4 years) were studied. None of the subjects had a history of hypertension, diabetes, or cigarette smoking. All had normal fasting lipid profiles. No subject was receiving medications, including estrogens, oral contraceptives, aspirin, or vitamin supplements. The study was reviewed and approved by the Institutional Review Board at the University of Missouri—Kansas City School of Medicine. All subjects were enrolled after giving signed, voluntary written informed consent.

2.2. Methods

On entry into the study, each subject was asked to fill out a detailed health questionnaire, detailing personal medical history; family history of hypertension, hyperlipidemia, coronary artery disease (CAD), diabetes, stroke, or peripheral vascular disease; and social history, medication use, and exercise habits. Subjects ingested a high-fat meal (Egg McMuffin, Sausage McMuffin, 2 hash brown patties, and a noncaffeinated beverage) containing 3766 J, 110 g of carbohydrates, 50 g of fat, 14 g of saturated fat, and 255 mg of cholesterol; an isoenergetic low-fat/high-carbohydrate meal (Frosted Flakes [Kellogg Company, Battle Creek, Mich], skimmed milk, and orange juice) containing 3682 J, 204 g carbohydrate, 0 g fat, 16 g protein, and 5 mg cholesterol; or the high-fat meal preceded by single doses of vitamin C (1000 mg of ascorbic acid) and vitamin E capsules (800 IU), as previously described [11,12]. Meals were administered in random order at least 1 week apart.

Measurements of vascular compliance, serum TG, glucose, and insulin were obtained in the fasting state and at hourly intervals for 6 hours after meal ingestion. We obtained blood pressure and heart rate by oscillometry, whereas large and small vessel elasticity indices were measured by analysis of the diastolic arterial pulse waveform using the HDI Pulse Wave Research Cardiovascular Profiling Instrument (Hypertension Diagnostics, Inc, Eagan, Minn). With this technique, the pulse contour is recorded noninvasively at the radial artery by aplanation tonometry [19]. The morphology of the arterial pulse contour can be separated by a computer algorithm into an exponential diastolic decay generated by the release of blood from the large arteries and a sinusoidal wave arising from peripheral wave reflections. The diastolic decay is a function of large artery compliance (C_1), whereas reflections or oscillations represent the compliance characteristics of the resistance vessels and branch points (C_2) [20-25]. The method has good reproducibility and correlates with invasive measures of arterial compliance [20].

Serum insulin was measured by radioimmunoassay. Serum glucose and lipids (fasting total cholesterol, TG, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C]) were determined by standard laboratory techniques. The homeostasis model assessment of insulin resistance ($HOMA_{IR}$) insulin sensitivity index was calculated for each subject based on fasting glucose and insulin values using the $HOMA_2$ calculator made available by the original authors of the index at http://www.dtu.ox.ac.uk/homa [26]. Areas under curve (AUCs) for glucose, insulin, and TG were calculated by the trapezoidal rule [27].

Plasma NO metabolites (nitrites and nitrates [NOx]) were estimated by the Griess method [3] before meals and at the time of the maximal postprandial change in vascular compliance for each subject.

2.3. Statistical analysis

Group values are expressed as mean ± SEM. Statistical change was analyzed by unpaired Student *t* test or by analysis of variance (ANOVA) for repeated measures, where appropriate. $P < .05$ was considered significant. Statistical analysis was accomplished with the use of the JMP statistical software program (SAS Institute Inc, Cary, NC).

3. Results

3.1. Effects on small (C_2) and large (C_1) artery compliance indices

A retrospective analysis of vascular compliance responses in the entire group of subjects revealed 2 subgroups, one in which C_2 fell after the high-fat meal and another in which C_2 either remained unchanged or rose. Those in whom C_2 declined by 20% or more at 2 or more time points within 4 hours of the ingestion of the high-fat meal were defined as "fat reactors." In these subjects (n = 8), mean C_2 fell from 9.2 ± 0.9 to 7.4 ± 0.9 mL/mm Hg × 100 after the high-fat meal and remained below baseline for 6 hours ($P <$ .0001 by ANOVA). In the remaining 10 subjects ("non-

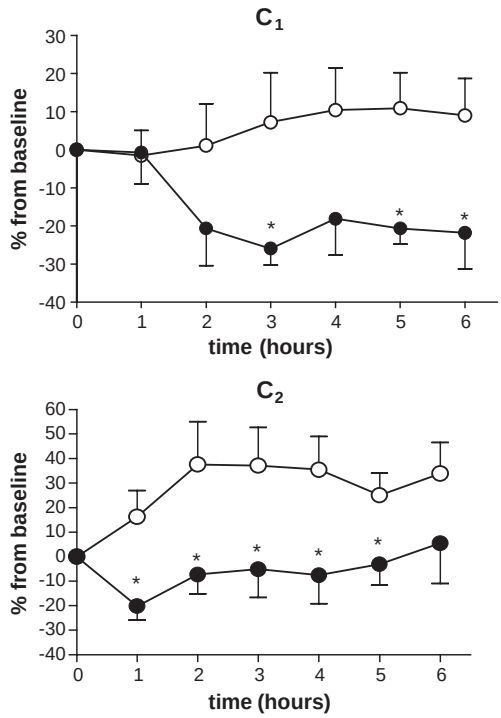

Fig. 1. C_1 and C_2 percent changes from baseline after a high-fat meal, in fat reactors (closed symbols) compared with nonreactors (open symbols). Asterisk indicates $P < .05$ between groups for the high-fat meal.

reactors"), mean C_2 rose from 7.0 ± 0.9 to 9.1 ± 1.7 mL/mm Hg × 100 at 2 hours and remained above baseline for 6 hours. Mean premeal C_2 did not differ between fat reactors and nonreactors.

C_1 decreased in fat reactors from 20.9 ± 1.8 to 15.5 ± 1.2 mL/mm Hg × 10 by 2 hours after fat loading, a reduction that was sustained for an additional 4 hours ($P < .005$ by ANOVA for repeated measures), whereas in nonreactors, mean C_1 fell slightly from 18.4 ± 1.8 to 16.4 ± 2.0 mL/mm Hg ×10 at 1 hour, but did not differ significantly from baseline during the remaining 5-hour postprandial period.

Table 2
Demographics of subjects and baseline cardiovascular parameters

Group	Total	Fat reactors	NonrFSeactors
n	18	8	10
Male/female	7/11	4/4	3/7
Age (y)	20.8 ± 0.2	21.2 ± 0.5	20.4 ± 0.5
Weight (kg)	68.6 ± 1.8	67.8 ± 4.1	69.1 ± 4.8
Height (cm)	171 ± 1	173 ± 4	170 ± 3
BMI (kg/m^2)	23.1 ± 0.3	22.5 ± 0.5	23.6 ± 1
Family history of CVD	5/18	2/8	3/10
SBP (mm Hg)[a]	116 ± 2	119 ± 3*	114 ± 1
DBP (mm Hg)[a]	66 ± 1	69 ± 1**	64 ± 1
Heart rate (bpm)[a]	63 ± 1	66 ± 2**	61 ± 2
C_1 (mL/mm Hg × 10)[a]	17.7 ± 0.6	17.7 ± 0.9	17.8 ± 0.9
C_2 (mL/mm Hg × 100)[a]	8.0 ± 0.3	8.5 ± 0.4	7.6 ± 0.4

bpm indicates beats per minute.
[a] Means of 3 premeal values.
* $P = .06$ vs nonreactors.
** $P < .05$ vs nonreactors.

Because of the differences in mean baseline C_1 and C_2 values, we further expressed compliance as percent change from baseline (Fig. 1; Table 1). After the high-fat meal, significant between-group differences were found in C_1 at 3, 5, and 6 hours and in C_2 at all post–meal time points up to 5 hours. Vitamin pretreatment blunted the fat-induced reduction in C_1 in fat reactors, but did not affect C_2 (Table 1). After the low-fat meal, C_2 increased by more than 15% after the first hour in both fat reactors and nonreactors, whereas C_1 showed little or no rise (Table 1). There were no significant intergroup differences in either C_1 or C_2.

3.2. Demographic characteristics

Fat reactors did not differ significantly from nonreactors in age, weight, height, or body mass index (BMI) (Table 2). However, diastolic blood pressure (DBP) and heart rate were significantly greater ($P < .05$) and systolic blood pressure

Table 1
Changes in large artery elasticity (C_1) and small artery elasticity (C_2) (expressed as percent change compared with baseline) in fat reactors compared with nonreactors after high-carbohydrate and high-fat meals, with and without vitamins

			Time point						
			0 h	1 h	2 h	3 h	4 h	5 h	6 h
High-fat meal	C_1	FR	0	−0.7 ± 8.3	−20.7 ± 9.7	−25.9 ± 4.3*	−18.1 ± 8.9	−20.7 ± 4.1*	−21.8 ± 9.5*
		NR	0	−1.3 ± 6.6	−0.8 ± 10.9	6.8 ± 13.0	9.8 ± 11.1	10.3 ± 9.3	8.7 ± 9.7
	C_2	FR	0	−20.1 ± 5.8*	−7.3 ± 7.9*	−5.1 ± 11.4*	−7.6 ± 11.6*	−3.1 ± 8.6*	5.5 ± 16.5
		NR	0	16.3 ± 10.7	37.7 ± 17.4	37.2 ± 15.5	35.6 ± 13.5	25.1 ± 9.1	33.9 ± 12.8
High-fat meal + vitamins C, E	C_1	FR	0	−5.6 ± 14.4	−5.7 ± 5.7	14.6 ± 20.1	4.4 ± 7.0	21.9 ± 12.2	0.6 ± 9.8
		NR	0	−8.3 ± 9.1	−1.7 ± 4.5	1.0 ± 8.7	2.9 ± 7.1	9.1 ± 11.0	−2.4 ± 9.8
	C_2	FR	0	−4.9 ± 20.3	−3.1 ± 10.9	−3.5 ± 9.7	−5.4 ± 12.1	5.7 ± 10.6**	−6.1 ± 11.9
		NR	0	−1.0 ± 16.7	12.8 ± 12.5	14.7 ± 9.7	−0.3 ± 7.5**	7.7 ± 8.7	−2.1 ± 18.3
Low-fat meal	C_1	FR	0	−11.8 ± 6.0	−0.7 ± 12.8	2.6 ± 13.7	14.0 ± 15.7	4.2 ± 3.9	9.3 ± 4.3
		NR	0	5.8 ± 8.4	−0.2 ± 8.3	2.0 ± 10.1	−4.9 ± 6.8	6.8 ± 8.6	−2.7 ± 6.8
	C_2	FR	0	15.6 ± 10.5	20.9 ± 15.0	14.4 ± 15.5	16.8 ± 13.5**	14.3 ± 11.8**	15.1 ± 13.0**
		NR	0	15.5 ± 10.5	14.7 ± 14.2	14.2 ± 16.2	16.2 ± 14.0	7.4 ± 10.3	3.2 ± 8.7**

FR indicates fat reactors; NR, nonreactors.
* $P < .05$ vs nonreactors (at same time point and same meal).
** $P < .05$ vs same group after high-fat meal.

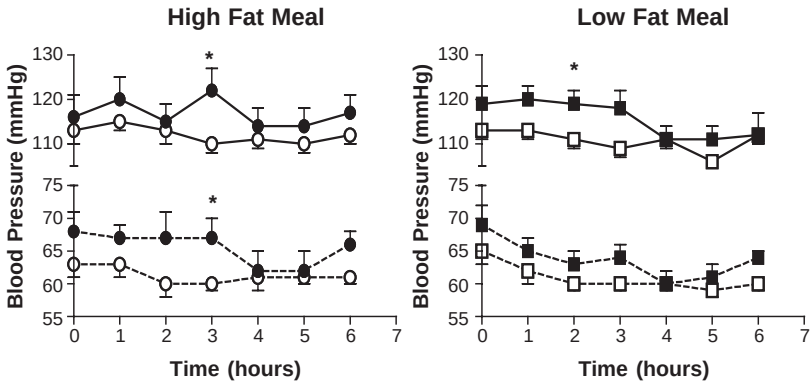

Fig. 2. Systolic blood pressure (continuous lines) and DBP (dashed lines) in fat reactors (closed symbols) and nonreactors (open symbols) after high-fat meal (circles) compared with high-carbohydrate meal (squares). Asterisk indicates $P < .05$ between the 2 groups.

(SBP) was marginally higher in fat reactors ($P = .06$). There were no differences in the incidence of a family history of hypertension, diabetes, CAD, stroke, or peripheral vascular disease between fat reactors and nonreactors (Table 2).

3.3. Hemodynamic effects of meals

Although mean SBP and DBP values were higher in fat reactors compared with nonreactors at nearly all time points after each meal (Fig. 2), significant differences were seen only at 3 hours after the high-fat meal (122 ± 5 vs 110 ± 2 mm Hg for SBP and 67 ± 3 vs 60 ± 1 mm Hg for DBP, respectively; $P < .05$); at 2 hours after the low-fat meal (119 ± 3 vs 111 ± 2 mm Hg for SBP; $P < .05$); and at 1 and 2 hours after the high-fat meal with vitamin pretreatment (70 ± 3 vs 63 ± 2 and 66 ± 1 vs 66 ± 2 mm Hg for DBP; $P < .05$).

3.4. Metabolic parameters

Screening mean serum total cholesterol, LDL-C, and HDL-C were within the normal range and did not differ significantly between fat reactors and nonreactors (Table 3). However, the average basal serum TG was significantly higher in fat reactors (96 ± 8 vs 78 ± 5 mg/dL, $P < .02$). Fasting blood glucose (87 ± 2 vs 81 ± 2 mg/dL, $P < .02$) and serum insulin values (15.9 ± 1.1 vs 13.1 ± 0.6 μU/mL, $P < .05$) were also significantly higher in reactors than in nonreactors. Thus, the $HOMA_{IR}$ index showed increased IR in fat reactors (1.7 ± 0.6 vs 1.4 ± 0.3, $P < .05$) (Table 3). After the high-fat meal, peak serum TG levels were 174 ± 29 mg/dL at 3 hours in fat reactors and 122 ± 10 mg/dL at 2 hours in nonreactors (Table 4; Fig. 3). Triglyceride levels were significantly higher in fat reactors at 3, 4, and 5 hours postprandially. The AUC for TG after the high-fat meal was significantly greater in fat reactors (852 ± 112 vs 615 ± 46, $P < .05$). Vitamin pretreatment did not alter the serum TG after the high-fat meal in either fat reactors or nonreactors (Table 4). After both the high-fat and low-fat (high-carbohydrate) meals, serum insulin increased in fat reactors compared with nonreactors (AUCs for insulin, 225 ± 37 vs 159 ± 20 and 298 ± 57 vs 223 ± 33, respectively; $P < .05$ for each), whereas blood glucose levels did not differ between groups after either meal (Table 4; Fig. 4). With antioxidant vitamin pretreatment, we found no difference between insulin AUCs in the 2 groups (222 ± 35 and 176 ± 27, respectively). After the high-carbohydrate meal, mean serum glucose rose from 92 ± 5 to 142 ± 20 mg/dL at 1 hour in fat reactors and from 82 ± 2 to 106 ± 10 mg/dL in nonreactors; serum insulin was significantly higher in fat reactors at 2 hours ($P < .05$), but glucose AUCs did not differ significantly between groups (Table 4).

In the fasting state, serum insulin strongly correlated with both C_2 ($r = 0.662$, $P < .02$) and C_1 ($r = 0.488$, $P < .05$) in nonreactors, but no correlation was present in fat reactors (Fig. 5), suggesting that fat reactors are resistant to the vasodilatory properties of insulin. Postprandial insulin and TG levels after the high-fat meal correlated strongly, both in nonreactors ($r = 0.416$, $P < .0001$) and in reactors ($r = 0.346$, $P < .005$).

3.5. Effects of meals on plasma NOx

Plasma NOx decreased from 41.1 ± 5.6 to 33.0 ± 2.5 μmol/L in fat reactors and from 33.5 ± 2.9 to 31.8 ± 2.6 μmol/L in nonreactors. The percentage decrease was significantly greater in fat reactors (17.0% ± 5.1% vs 4.8% ± 2.1%, $P < .05$). With antioxidant vitamins, plasma NOx declined from 35.8 ± 3.7 to 31.8 ± 2.7 μmol/L in fat reactors and from 35.7 ± 2.5 to 33.6 ± 1.7 μmol/L in nonreactors,

Table 3
Baseline metabolic and cardiovascular parameters

	Total	Fat reactors	Nonreactors
n	18	8	10
Blood glucose (mg/dL)	84 ± 1	87 ± 2*	81 ± 2
Serum insulin (μU/mL)	14.3 ± 0.6	15.9 ± 1.1*	13.1 ± 0.6
$HOMA_{IR}$ (arbitrary units)	1.6 ± 0.5	1.7 ± 0.6*	1.4 ± 0.3
Cholesterol (mg/dL)	169 ± 10	181 ± 15	157 ± 13
TGs (mg/dL)	86 ± 5	96 ± 8*	78 ± 5
HDL-C (mg/dL)	50 ± 3	52 ± 5	49 ± 4
LDL-C (mg/dL)	103 ± 9	111 ± 14	95 ± 12

Parameters are means of 3 premeal values.
* $P < .05$ vs nonreactors.

Table 4
Blood glucose, insulin, and TGs and AUC after high-carbohydrate and high-fat meals, with and without vitamins in fat reactors and nonreactors

			Time point							
			0 h	1 h	2 h	3 h	4 h	5 h	6 h	AUC (arbitrary units)
High-fat meal	Insulin (μU/mL)	FR	15 ± 2	63 ± 16	42 ± 7	43 ± 11	34 ± 5*	25 ± 5	21 ± 4	225 ± 37*
		NR	13 ± 1	40 ± 7	29 ± 4	25 ± 3	19 ± 1	18 ± 2	14 ± 1	144 ± 14
	Glucose (mg/dL)	FR	85 ± 2	98 ± 9	87 ± 4	89 ± 2	92 ± 5	85 ± 2	86 ± 2	536 ± 19
		NR	82 ± 3	83 ± 9	80 ± 4	84 ± 3	82 ± 4	88 ± 2	85 ± 2	501 ± 17
	TG (mg/dL)	FR	94 ± 12	115 ± 12	149 ± 23	174 ± 29*	159 ± 23*	147 ± 21*	122 ± 18	852 ± 112*
		NR	72 ± 7	103 ± 11	122 ± 10	110 ± 8	108 ± 10	95 ± 8	85 ± 8	615 ± 46
High-fat meal + vitamins C, E	Insulin (μU/mL)	FR	16 ± 2	57 ± 12	51 ± 8*	44 ± 8	27 ± 5	26 ± 5	18 ± 2	222 ± 35
		NR	13 ± 1	37 ± 64	29 ± 3	31 ± 6	27 ± 4	21 ± 3	14 ± 1	157 ± 20
	Glucose (mg/dL)	FR	85 ± 1	105 ± 1*	93 ± 1	94 ± 1	89 ± 1	89 ± 1	86 ± 1	555 ± 23
		NR	79 ± 1	82 ± 4	85 ± 2	88 ± 4	85 ± 2	87 ± 1	83 ± 2	509 ± 12
	TG (mg/dL)	FR	111 ± 18	115 ± 13	146 ± 15	147 ± 18	126 ± 20	112 ± 16	96 ± 13	725 ± 88
		NR	75 ± 7	87 ± 8	115 ± 8	122 ± 12	115 ± 14	96 ± 12	78 ± 11	611 ± 53
Low-fat meal	Insulin (μU/mL)	FR	15 ± 2	103 ± 26	80 ± 14*	53 ± 12	30 ± 6	18 ± 3	14 ± 2	297 ± 57*
		NR	14 ± 1	60 ± 7	48 ± 7	34 ± 7	25 ± 4	16 ± 2	13 ± 2	195 ± 17
	Glucose (mg/dL)	FR	92 ± 4	142 ± 20	110 ± 14	87 ± 7	80 ± 4	79 ± 3	79 ± 3	572 ± 42
		NR	82 ± 2	103 ± 10	95 ± 5	82 ± 4	83 ± 3	78 ± 4	78 ± 2	520 ± 12
	TG (mg/dL)	FR	91 ± 9	91 ± 10	82 ± 7	80 ± 7	80 ± 8	72 ± 6	80 ± 6	490 ± 37
		NR	88 ± 11	88 ± 9	76 ± 9	75 ± 9	74 ± 8	79 ± 9	77 ± 7	470 ± 50

* $P < .05$ vs nonreactors, same meal.

reductions of 9.8% ± 3.8% and 4.1% ± 3.7%, which were not significant. After the carbohydrate meal, plasma NOx decreased from 35.3 ± 1.9 to 30.9 ± 1.6 μmol/L in fat reactors and from 37.1 ± 3.4 to 32.9 ± 2.1 μmol/L in nonreactors. The percentage decrease was similar in both groups (11.8% ± 4.2% vs 11.9% ± 3.2%). These effects of high fat on NO metabolites are consistent with the role of NO on mediating arterial compliance.

4. Discussion

Based on a retrospective division of the subjects, we have shown that in the subgroup of 8 fat reactors, representing 44.4% of the subjects, a single high-fat meal can reduce both C_1 and C_2 for up to 6 hours. Although within the normal range, fasting serum glucose, insulin, $HOMA_{IR}$, and TG were significantly higher in fat reactors. After the fat load, serum insulin, TG, and their respective AUCs were significantly higher in fat reactors, confirming that fat reactors were more insulin resistant then their nonreactor counterparts. Serum glucose was also consistently higher at all time points in fat reactors after the high-fat load, but the difference did not reach statistical significance. Our subjects did not fulfill all criteria of the metabolic syndrome, but fat reactors show the presence of some markers of increased IR compared with

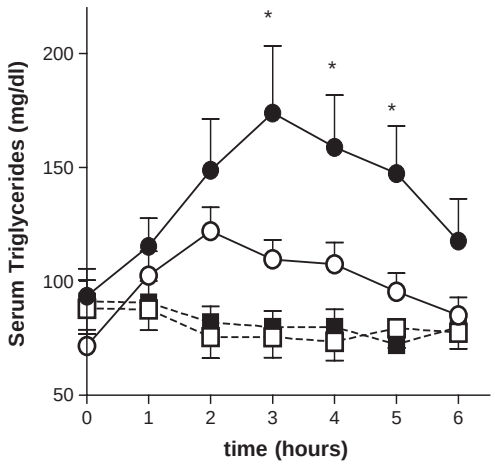

Fig. 3. Triglyceride changes after the high-fat meal (continuous lines) and low-fat meal (dashed lines) in fat reactors (solid symbols) compared with nonreactors (open symbols). Asterisk indicates $P < .05$ for fat reactors compared with nonreactors during the high-fat meal.

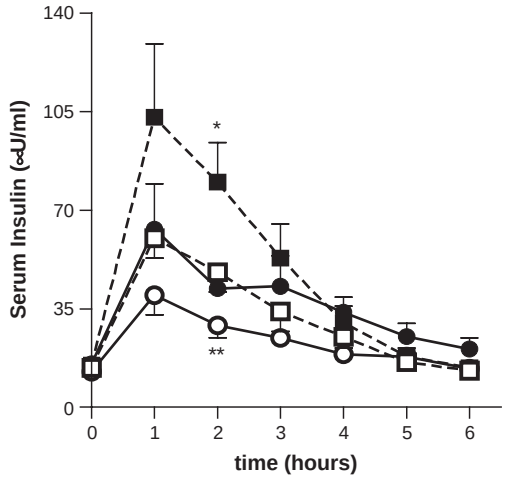

Fig. 4. Serum insulin changes after the high carbohydrate meal (dashed lines) and high-fat meal (continuous lines) in fat reactors (solid symbols) compared with nonreactors (open symbols). Asterisk indicates $P < .05$ between groups for the low-fat meal; double asterisk, $P < .05$ between groups for the high-fat meal.

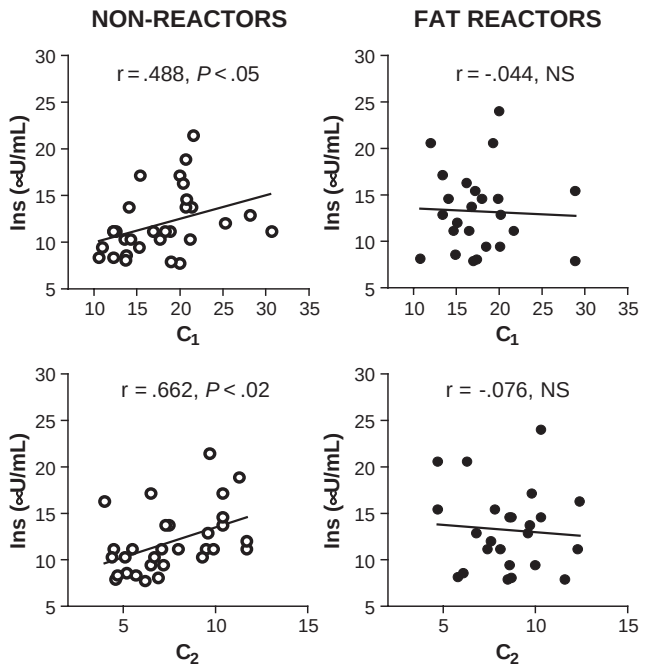

Fig. 5. Insulin correlation with large (C_1) and small (C_2) artery compliance in nonreactors (open circles) compared with fat reactors (closed circles).

nonreactors. The National Health and Nutrition Examination Survey reported the prevalence of the fully developed metabolic syndrome to be 4% to 5% in persons 20 to 30 years old, but a much larger proportion in the general population present with only some of its elements [28].

There was a strong correlation between postprandial insulin and TG levels in both groups, similar to that found in a large subgroup of young subjects in the Bogalusa Heart Study [29]. Among young adults in this study, childhood levels of serum TG, HDL-C, and especially SBP values were found to be independent predictors of vascular stiffness [30]. The powerful positive correlation between insulin and vascular compliance in fasting nonreactors, and the absence of this correlation in fat reactors, favors the presence of IR in the latter group (Fig. 5).

In fat reactors SBP, DBP, and pulse rate were significantly increased in the fasting state, a finding that also supports an insulin-resistant state in these subjects. Indeed, the association between increased sympathetic tone, hypertriglyceridemia, hypertension, and the metabolic syndrome is well established [31] and characterizes "metabolically obese normal weight individuals" who are considered prone to develop CVD [32]. Blood pressure increased significantly in fat reactors within 1 to 3 hours of food ingestion compared with nonreactors (Fig. 2). The findings suggest that the expected vasodilatory effect of postprandial insulin secretion was blunted in fat reactors, as opposed to nonreactors, whose blood pressure was the same or decreased slightly after a meal. Insulin is known to act as a vasodilator through endothelial nitric oxide synthase (eNOS) stimulation of NO production [33]. Although both high-fat and high-carbohydrate meals raised serum insulin levels, only the high-fat meal significantly increased serum TG levels and reduced vascular compliance in fat reactors. Thus, decreased vascular compliance appears to be related to IR- and/or TG-mediated endothelial dysfunction. Insulin resistance in skeletal muscle is known to be associated with increased TG levels, and plasma free fatty acids play a pivotal role in the further development of diabetes by impairing insulin signaling pathways and increasing production of inflammatory mediators [34]. Hepatic lipoprotein lipase (LPL) is known to be regulated by insulin, and LPL mass was shown to be inversely correlated to $HOMA_{IR}$ in normal adults, subjects with impaired glucose tolerance, and diabetic patients [35]. Lower LPL mass would thus explain high TG postprandial peaks and high basal TG levels in fat reactors. Genetic variants of LPL could also be involved in the pathogenesis of both IR and atherosclerosis/CAD [36], but their evaluation was beyond the scope of the present study.

Hypertriglyceridemia can induce endothelial dysfunction through multiple mechanisms [37] that include increased reactive oxygen species production by polymorphonuclear leukocytes and endothelial cells [3], scavenging of NO by superoxide anions with production of peroxynitrite [16], induction of adhesion molecules, and stimulation of the production of proinflammatory mediators [38,39]. The postprandial decrease in plasma and urinary NO metabolites allows an indirect evaluation of NO inactivation and sequestration by free radicals. Previously, it has been shown that the decrease in NOx is associated with increased tissue nitrotyrosine [40,41]. The greater decrease of plasma NOx in fat reactors suggests that these subjects may belong to a "pro-oxidative phenotype" [42], with increased free radical production in response to a fat load, compared with nonreactors. Therefore, our findings suggest that in subjects with IR, elevated TG levels can "tip the balance" in favor of superoxide anion production and destruction of NO, such that the normal NO-mediated vasodilatory response to insulin is abrogated [7]. Using similar comparisons between meals of varying fat content, other clinical studies agree with our findings on differing effects of macronutrients on vascular compliance [15,16] and on leukocyte superoxide production [4].

In our subjects, the decrease of C_1 was only partially prevented in the fat reactors by premeal administration of the antioxidant vitamins C and E, whereas C_2 was not significantly improved. In healthy subjects, a single dose of antioxidant vitamins can attenuate fat meal–stimulated increases in markers of endothelial function [1] and partially restore the vascular response to L-arginine, a precursor of NO [43]. In a study of 20 healthy, middle-aged adults, it was also found that pretreatment with a single dose of vitamin C 1000 mg and vitamin E 800 IU blocked the reduction in flow-mediated vasodilation induced by a high-fat meal [11].

Although experimental and observational studies suggest that antioxidant vitamins may increase vascular production of NO and thus reduce endothelial dysfunction [44],

evidence from clinical trials has not supported these putative benefits. In a recent study [45], 8 weeks of vitamin C and E supplementation did not influence coronary or peripheral endothelial function in subjects with CAD. In contrast, it was reported that high doses of vitamin C monotherapy improved hyperemic vasodilation of the brachial circulation in patients with endothelial dysfunction and CAD [46]. Likewise, the results of the small, randomized, placebo-controlled Endothelial Assessment of Risk from Lipids in Youth trial in children with familial hyperlipidemia showed that supplementation with vitamins C and E restored impaired endothelial function [47].

The immediate response of large vessel reactivity to antioxidants is in accordance with experimental studies in which altered aortic reactivity in animals fed a high-fat diet was readily reversed by incubation with varying concentrations of vitamin C or high concentrations of vitamin E solutions [2]. In this study, both vitamins C and E reduced nicotinamide adenosine dinucleotide phosphate [NAD(P)H] activity and superoxide anion production and increased eNOS activity and NO synthesis and thus had an immediate effect on vascular reactivity. The discrepancies between the above-mentioned results and those of the present study could be due to differences in designs, ages of the groups studied, or the presence of associated pathology such as diabetes, all of which can significantly influence vascular responses. Fat reactors may also have had lower baseline plasma levels of antioxidant vitamins because only a small percentage (20%-36%) of American adolescents and children consume the recommended daily intake of fresh fruits and vegetables [48].

Our study has several limitations. The relatively small number of subjects does not allow a definitive conclusion on the effect of demographic parameters such as sex, family history of metabolic syndrome/diabetes, or CVD on vascular compliance; recent papers suggest that healthy nonobese offspring of diabetic patients have increased vascular stiffness [49]. Also, the normal mean BMI does not exclude the possibility of increased mesenteric fat in fat reactors [50] because abdominal imaging was not performed. Nonreactors may represent more insulin-sensitive subjects with a particularly favorable metabolic profile; thus, they may be protected against TG-induced endothelial dysfunction after a fat load, as revealed by lower TG peak, and/or may have had a higher intake of antioxidant vitamins that provided a stronger defense against the oxidative stress of a high-fat meal.

In conclusion, in a young healthy population, evaluation of vascular compliance after fat loading can generate hypotheses as to mechanisms by which risk factors such as postprandial hypertriglyceridemia induce endothelial dysfunction. We propose that changes in arterial elasticity, which can be easily and noninvasively evaluated, may help identify subjects with an abnormal response to a high-fat meal as a marker of the “increased oxidative stress phenotype,” who might harbor IR and endothelial dysfunction.

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