Impaired hemodynamic response to meal intake in insulin-resistant subjects: an impedance cardiography approach

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ABSTRACT

Background: In the postprandial state, insulin regulates metabolic and cardiovascular responses. In insulin resistance, the insulin action is impaired at both levels. However, postprandial hemodynamic responses are poorly characterized in this setting.

Objective: We investigated fasting and postprandial cardiac and vascular hemodynamic responses in subjects with and without insulin resistance.

Design: Sixty-six atherosclerosis-free, healthy volunteers were studied in a fasted state and ≤180 min after ingestion of a mixed meal. The insulin sensitivity index was determined by using a minimal model analysis; hemodynamic response was monitored by using continuous impedance cardiography that allowed a reliable beat-to-beat noninvasive evaluation of stroke volume, cardiac contractility, and several derived variables.

Results: Subjects were divided into insulin-resistant (IR; n = 33) and insulin-sensitive (IS; n = 33) groups. After fasting, IR subjects had significantly higher values of systolic and diastolic blood pressures and the systemic vascular resistance index (SVRI) than did IS subjects. In the postprandial state, acute vasodilatation was comparable and synchronous (at 30 min) in IR and IS subjects (P = 0.209), but subsequent vascular tone recovery (30–180 min) was significantly impaired in IR subjects (P = 0.018), even after adjustment for age and sex (P = 0.031). Hemodynamic dysregulation was directly correlated with metabolic disturbances in the postprandial state. In basal and postprandial states, hemodynamic variables related to cardiac function were not significantly different in IR and IS subjects.

Conclusions: IR subjects had a worse fasting vascular performance than did IS subjects. In the postprandial phase, insulin resistance was associated with a shorter duration of vasodilatation in the absence of an altered cardiac performance. Peripheral hemodynamic alterations in fasting and postprandial states may have a negative effect on cardiovascular performance in IR patients.

INTRODUCTION

The postprandial phase involves complex neurohormonal, metabolic, and cardiovascular interactions (1). A pivotal role in the regulation of the postprandial phase is played by insulin, which mediates metabolic and hemodynamic actions (2–4) and achieves the so-called hemodynamic-metabolic coupling. Food ingestion also contributes to modulate heart and blood vessel responses (5). In the insulin-resistant (IR) state, the metabolic and vascular milieu are altered (6, 7), which thus determine the unfavorable proatherogenic state, which has been thoroughly documented (8, 9).

However, little is known about the postprandial hemodynamic response in IR patients. Even subclinical pathophysiologic alterations may trigger a complex series of events that lead to vascular disease in these patients. It was previously shown that, in the postprandial phase, the circulatory response may be impaired in subjects with insulin resistance, even without subclinical atherosclerosis (10–12). The paucity of studies on the hemodynamic response is mainly because of the need of cumbersome and frequently invasive measurements. Among noninvasive techniques, thoracic bioimpedance cardiography (ICG) is an attractive operator-independent and cost-effective method. ICG was developed by the National Aeronautics and Space Administration in the 1960s to monitor cardiac output in astronauts (13), and this approach has been used in critically ill patients (14, 15) and in patients with heart failure (16). The ICG signal is obtained from thoracic impedance detected at beat-to-beat intervals; changes in thorax impedance during the cardiac cycle allow for the calculation of stroke volume, cardiac output, and indicators of cardiac contractility (17). The quantitative analysis of ICG signals and their relations with insulin resistance are unexplored.

Therefore, in this study we investigated the ICG-derived hemodynamic data in a fasting state and their temporal profiles in postprandial condition in subjects with and without insulin resistance.

SUBJECTS AND METHODS

Subjects

From January 2007 to February 2009, healthy volunteers were recruited by advertisement. Inclusion criteria were as follows:

1. From the Departments of Clinical and Experimental Medicine (SVdK, GPF, FB, ER, GC, and AA) and Information Engineering (SG, GS, CC), Padova University, Padova, Italy, and the Department of Cardiology, SS Giovanni e Paolo Hospital, Venezia, Italy (MB).
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men and women aged >20 to <65 y; an absence of known diseases, apart from borderline-mild arterial hypertension; provision of informed consent to participate in the study. Exclusion criteria were as follows: age <20 or >65 y, known chronic diseases, and ongoing therapy (except for antihypertensive drugs). Five subjects were receiving antihypertensive therapy (low doses of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), which was withdrawn ≥3 d before the study. To exclude cardiovascular diseases, individuals were preliminarily subjected to 1) a carotid ultrasound examination with a measure of intima-media thickness, 2) measurement of the ankle-brachial index, and 3) the Rose angina questionnaire. Individuals with clinical or subclinical atherosclerotic disease, which was defined as the presence of carotid plaques, a carotid intima-media thickness >0.9 mm, claudication, an ankle-brachial index <0.9, or an abnormal angina questionnaire were excluded. With these criteria, 66 patients (50 men and 16 women) were finally enrolled in the study.

Study protocol
The experimental protocol was approved by the local ethical committee, and all subjects gave their informed written consent to participate in the study. Participants were studied in a fasting state at 0830 while comfortably lying in a bed in a temperature controlled room. After collection of anthropometric and blood pressure measurements, a 20-G cannula was inserted in a vein of the right arm for blood sample collection and determination of glucose, insulin, C-peptide, and free fatty acid (FFA) concentrations and a lipid profile. After 20 min of resting, continuous ICG monitoring (Niccomo; Medis, Ilmenau, Germany) was started to monitor hemodynamic variables in a fasting condition for a 20-min basal period and during the subsequent 180 min after ingestion of a mixed meal [Clinutren, 400 mL (55% carbohydrate, 15% protein, and 30% fat); Nestlé, Vevey, Suisse] which was performed in 10 min. Blood samples were drawn at −5, 0, 10, 20, 30, 60, 90, 120, 150, and 180 min for the assessment of glucose, insulin, C-peptide, and FFA concentrations.

Assessment of insulin sensitivity
Insulin sensitivity [defined by using the insulin sensitivity index (Si) and expressed as 10⁻³ dL · kg⁻¹ · min⁻¹ per μU/mL] was estimated from plasma glucose and insulin concentrations measured during the meal test by using the oral glucose minimal model (18). The Si measures the overall effect of insulin to stimulate glucose disposal and to inhibit glucose production.

ICG
The ICG methodology used in this study was similar to that used in previous clinical studies (16, 19–23). Four couples of electrodes were placed at the neck and thorax of each subject to detect variations in thoracic bioimpedance. The system was coupled with a standard sphygmomanometer transducer that measured blood pressure at given intervals. The Medis Niccomo ICG device processed these changes with a dedicated algorithm (physiologic adaptive signal analysis) and noninvasively and continuously provided the following hemodynamic variables: arterial systolic, diastolic, and mean blood pressures (at 15-min intervals); heart rate; stroke volume; cardiac index (cardiac output normalized for body surface area); left ventricular ejection time [LVET; the time interval from the opening to the closing of the aortic valve (ie, mechanical systole)]; left cardiac work index (LCWI), which reflected the myocardial oxygen demand; isovolumetric relaxation time (IVRT; the time from the aortic valve closure to the mitral valve opening), which reflected the diastolic function; and systemic vascular resistance index (SVRI). ICG variables were calculated by using the mean of 4-min beat-to-beat values at the end of the basal period (20 min) and continuously for the next 180 min after meal ingestion. The ICG technique has shown good reproducibility and variability values (24). After completion of the study protocol, original ICG recordings were downloaded in a personal computer for off-line analysis.

Doppler ultrasound measure of mesenteric blood flow
In a subgroup of 8 IR and 11 IS subjects, ultrasound examinations were performed with a Philips HDI 5000 Sono CT unit (Philips Medical Systems, Bothell, WA). The superior mesenteric artery (SMA) was examined in its long axis in the sagittal plane. The sampling cursor was placed within the diameter of the vessel at 2–3 cm distal to its origin, and the angle between the ultrasound beam and the SMA was kept at <60°. Then peak systolic velocity (PSV) was sampled at baseline and 60, 120, and 180 min after meal ingestion.

Analytic methods and calculation
Plasma glucose concentrations were measured by the glucose oxidase method with a glucose analyzer (Beckman, Albertville, MN). Plasma insulin and C-peptide concentrations were measured by using conventional radioimmunoassay. Total cholesterol, triglyceride, and FFA concentrations were measured with an enzymatic assay. HDL-cholesterol concentrations were measured by using polyethylene glycol precipitation with enzymatic quantitation.

Statistical analyses
Statistical analyses were completed with SPSS 15.0 for Windows software (SPSS Inc, Chicago, IL). Values were expressed as means ± SEs. Statistical analyses included 1) descriptive statistics, 2) a 2-tailed paired Student’s t test with Bonferroni correction for the evaluation of changes in hemodynamic variables in the postprandial phase compared with at baseline in all subjects, 3) a 2-tailed unpaired Student’s t test for comparison between IR and IS subjects, 4) analysis of variance for repeated measures (RM-ANOVA) to study postprandial differences between groups, and 5) a generalized linear model to analyze differences between IR and IS subjects in trends of repeated measures with adjustment for potential covariates, such as age and sex. Statistical significance was accepted at P < 0.05.

RESULTS
Anthropometric and fasting metabolic variables
Main demographic, clinical, and metabolic characteristics of the study population are summarized in Table 1. Subjects were classified as IR (n = 33) or IS (n = 33) subjects on the basis of the whole-population Si median value (7.27 × 10⁻⁴ dL · kg⁻¹ ·
min\(^{-1}\) per \(\mu\)U/mL). As expected, variables linked to insulin resistance, such as measures of adiposity, plasma glucose, insulin, and C-peptide concentrations, as well as triglyceride and HDL-cholesterol concentrations, were significantly different in IR than in IS subjects. The 2 groups also differed in age and sex distributions (ie, the IR group was composed of older subjects with a higher proportion of men).

**Fasting hemodynamic variables**

Hemodynamic variables and comparisons between IR and IS groups are summarized in Table 2. In fasting state, IR subjects showed significantly higher systolic and diastolic blood pressures and a higher SVRI than did IS subjects. All other variables showed no significant differences between IR and IS subjects.

**Postprandial metabolic variables**

Postmeal trends of glucose, insulin, C-peptide, and FFA concentrations observed in IR and IS groups are illustrated in Figure 1. As expected, except for FFA concentrations, curves were separated between IR and IS groups throughout the period of observation but significantly diverged \(\approx 30\) min after meal ingestion, which indicated that metabolic disturbances in these patients were more pronounced in the 30–180-min than in the 0–30-min postmeal period.

**Postprandial hemodynamic variables**

In the whole study population, we observed significant variations of cardiovascular variables after meal ingestion. There was a reduction in the mean blood pressure and SVRI and an increase in the stroke volume and cardiac index within the first 30 min. In particular, there was a descending phase in the SVRI from 0 to 30 min (acute vasodilation) and a recovery phase from \(\geq 30\) min. Other cardiac-function variables, such as LCWI, LVET, and IVRT, showed significant changes in the later postmeal phase than at baseline (Figure 2).

We compared postmeal percentage changes of hemodynamic variables with respect to baseline variables in IR compared with in IS groups. With consideration of the entire postmeal phase (0–180 min), there were no significant differences between IR and IS groups. We separately analyzed the acute postmeal phase (0–30 min) and the later postmeal phase (30–180 min). The acute postmeal maximal vasodilatation was similar in both groups (SVRI: \(-12.7 \pm 2.5\%\) in the IR group and \(-13.6 \pm 2.5\%\) in the IS group).

### Table 1

Main demographic, clinical, and metabolic variables in all, insulin-resistant (IR), and insulin-sensitive (IS) subjects in the fasting condition

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 66)</th>
<th>IR (n = 33)</th>
<th>IS (n = 33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women (n)</td>
<td>50/16</td>
<td>30/3</td>
<td>20/13</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (y)</td>
<td>48 ± 1.0</td>
<td>52 ± 1.2</td>
<td>44 ± 1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>95 ± 1.8</td>
<td>104 ± 2.5</td>
<td>88 ± 2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>26.8 ± 0.5</td>
<td>29.5 ± 0.8</td>
<td>2.4 ± 0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>91 ± 2.9</td>
<td>100 ± 4.8</td>
<td>82 ± 2.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Insulin ((\mu)U/mL)</td>
<td>12 ± 0.9</td>
<td>17 ± 1.7</td>
<td>10 ± 1.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C-peptide (ng/mL)</td>
<td>1.9 ± 0.1</td>
<td>2.5 ± 0.3</td>
<td>1.3 ± 0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>129 ± 10.7</td>
<td>160 ± 18.0</td>
<td>97 ± 8.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>197 ± 3.30</td>
<td>202 ± 5.3</td>
<td>191 ± 4.8</td>
<td>0.126</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>48 ± 1.4</td>
<td>44 ± 2.0</td>
<td>51 ± 2.2</td>
<td>0.029</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>124 ± 2.9</td>
<td>129 ± 4.5</td>
<td>120 ± 4.7</td>
<td>0.186</td>
</tr>
<tr>
<td>FFA ((\mu)mol/L)</td>
<td>597 ± 37</td>
<td>642 ± 56</td>
<td>550 ± 46</td>
<td>0.217</td>
</tr>
<tr>
<td>Si ((10^{-4}) (\text{dl} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) per (\mu)U/mL)</td>
<td>10.4 ± 1.0</td>
<td>3.5 ± 0.4</td>
<td>17.8 ± 1.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^1\) All values are means ± SEs. FFA, free fatty acid; Si, insulin sensitivity index.

### Table 2

Baseline hemodynamic variables in all, insulin-resistant (IR), and insulin-sensitive (IS) subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 66)</th>
<th>IR (n = 33)</th>
<th>IS (n = 33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>69 ± 1.1</td>
<td>71 ± 1.3</td>
<td>68 ± 1.7</td>
<td>0.117</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>124 ± 1.9</td>
<td>131 ± 2.6</td>
<td>119 ± 2.4</td>
<td>0.003</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>81 ± 1.0</td>
<td>85 ± 1.5</td>
<td>78 ± 1.3</td>
<td>0.002</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>93.7 ± 1.3</td>
<td>96 ± 2.0</td>
<td>91 ± 1.5</td>
<td>0.027</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>91.7 ± 2.5</td>
<td>91 ± 3.2</td>
<td>92 ± 3.9</td>
<td>0.778</td>
</tr>
<tr>
<td>CI (L (\cdot) min(^{-1}) \cdot m(^{-2}))</td>
<td>3.22 ± 0.07</td>
<td>3.1 ± 0.9</td>
<td>3.3 ± 0.9</td>
<td>0.172</td>
</tr>
<tr>
<td>SVRI (dyn (\cdot) s (\cdot) cm(^{-5}) \cdot m(^{-2}))</td>
<td>2350 ± 78</td>
<td>2539 ± 124</td>
<td>2149 ± 78</td>
<td>0.011</td>
</tr>
<tr>
<td>LCWI (kg (\cdot) min (\cdot) m(^{-2}))</td>
<td>3.85 ± 0.75</td>
<td>3.8 ± 0.1</td>
<td>3.9 ± 0.1</td>
<td>0.927</td>
</tr>
<tr>
<td>LVET (ms)</td>
<td>318 ± 4.8</td>
<td>311 ± 6.0</td>
<td>325 ± 7.3</td>
<td>0.139</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>163 ± 4.8</td>
<td>163 ± 7.6</td>
<td>163 ± 5.4</td>
<td>0.993</td>
</tr>
</tbody>
</table>

\(^1\) All values are means ± SEs. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SV, stroke volume; CI, cardiac index; SVRI, systemic vascular resistance index; LCWI, left cardiac work index; LVET, left ventricular ejection time; IVRT, isovolumetric relaxation time.
IS group; RM-ANOVA P = 0.209) and was registered 30 min after meal ingestion (Figure 3). However, the vascular tone in the recovery phase (30–180 min) appeared significantly different and showed a more transient vasodilatation in IR than in IS subjects. IR subjects showed SVRI similar to baseline at 75 min, whereas in IS subjects, vasodilatation lasted until 180 min. On a generalized linear model, the difference in the 30–180-min SVRI trend between IR and IS groups remained significant after adjustment for age and sex (P = 0.031), which were different in the 2 groups but appeared not to be significant determinants of the SVRI trend.

Because hemodynamic differences between IR and IS groups occurred in the 30–180-min period, when metabolic differences were more pronounced, we analyzed relations between the IR and IS gaps of these variables. We showed a linear correlation between excess insulin release and excess SVRI in IR patients (r = 0.71, P = 0.02) (Figure 4). A similar correlation was shown between the mean Δ% SVRI and mean Δ% glucose (r = 0.56; P = 0.11) and mean Δ% percentage C-peptide (r = 0.70, P = 0.02). These associations indicated a link between metabolic and hemodynamic disturbances in IR patients that occurred ≥30 min after the meal.

We showed no other significant differences in hemodynamic changes between IR and IS groups in the postprandial phase. Specifically, variables primarily related to cardiac performance (eg, LVET and IVRT) showed nonsignificantly different variations in IR compared with IS subjects, either in the acute or later postmeal phases (not shown).

SMA blood flow

PSV in the SMA was sampled in a subgroup of 8 IR (7 men) and 11 IS (5 men) subjects. At baseline, PSV was not different between IR and IS subjects. At 60 min, PSV was significantly lower in IR than in IS subjects (P = 0.04) (Figure 3B).

DISCUSSION

In this study conducted in healthy individuals, we showed that insulin resistance was associated with a disturbed vasodilatory response between 30 and 180 min after ingestion of a mixed meal, which was synchronous with an exaggerated insulin response and defective glucose clearance.

Insulin resistance determines metabolic diseases and increased cardiovascular risk. Postprandial metabolic abnormalities, such as hyperglycemia, hyperlipemia, and oxidative stress, significantly contribute to the pathogenesis of atherosclerosis in prediabetes (25, 26). The postprandial state, which accounts for a major part of life during the day, is characterized by fluctuations of circulating metabolites that are tightly coupled with variations of hemodynamic variables. Because postprandial hemodynamic perturbations in IR subjects are poorly characterized, in this study, we noninvasively monitored these variables in fasting and postprandial conditions.

In the fasting condition, IR subjects had significantly higher arterial pressure and systemic vascular resistance than did IS subjects. These findings were consistent with an increased arterial stiffness (27) and abnormal endothelial vasodilatation and pulse wave velocity, as previously described in IR subjects (28). Importantly, although these studies (27, 28) analyzed different pathophysiologic perspectives of vascular resistance, they did not report salient clinical readouts. At variance, we were able to describe the time course of hemodynamic-response abnormalities in IR subjects after a physiologic stimulus, such as the ingestion of a meal.
The main determinants of blood pressure are vascular resistance \( (R) \) and cardiac output \( (Q) \) as follows:

\[
P = R \times Q
\]

The increased baseline arterial pressure documented in IR subjects in the absence of significant changes in cardiac output suggested an intrinsic alteration of the arterial resistance bed. The significant correlation we showed between baseline SVRI and basal insulin concentrations \((r = -0.244, P = 0.048)\) supported the link between insulin resistance and the vascular arterial bed. Although the correlation between insulin concentrations and SVRI was weak in the fasting condition, it was much stronger in the postprandial phase (Figure 4). Indeed, the major finding of this study concerned the postprandial state. After subjects ingested the meal, we documented modifications in cardiac-function variables; the stroke volume and cardiac index were...
significantly increased within the first 30 min. Other cardiac-performance variables showed later modifications that were consistent with slightly impaired diastolic (increased IVRT) and systolic (reduced LVET) functions and reduced cardiac work (LCWI). These observations indicate that the ingestion of a mixed meal represented an important physiologic stimulus that exerted significant modifications of the peripheral vasculature and heart function.

In the postprandial state, IR and IS patients showed 2 distinct trends of vascular resistance; although the timing and the degree of acute maximal vasodilatation were identical, the subsequent period of recovery from vasodilatation was significantly shorter in IR than in IS subjects. This observation implied that, despite a conserved acute postprandial vasodilatation in IR subjects, the later peripheral hemodynamic response was compromised. Our study could not provide a definite explanation for this behavior; however, the temporal association between the defective vascular tone recovery and alteration of metabolic variables suggested an impaired vascular-metabolic coupling in IR subjects. Previous studies have shown that insulin resistance was associated with an activated neuroendocrine adrenergic response and altered temporal pattern (29, 30). Furthermore, it was shown that impaired changes in the forearm blood flow response to insulin were related to insulin resistance (31).

Nevertheless, besides insulin, several other hormones elicited by a meal may contribute to the deranged vascular regulation in insulin resistance, such as leptin, glucagon-like peptide 1, ghrelin, and cholecystokinin, which mainly act on the splanchnic circulation (32, 33). After ingestion of a meal, changes in systemic vascular resistances likely reflect the vascular splanchnic response. This was confirmed by the observation in a subset of IR and IS subjects that an increase in mesenteric artery PSV was compromised in IR compared with in IS subjects. Postprandial vasodilatation is typically impaired in several peripheral arterial districts in IR subjects (10, 34, 35). In IR subjects, postprandial arterial relaxation, as measured with the augmentation index, which is an independent predictor of cardiovascular risk, was impaired (28, 36). We have also previously shown that the cardiac microcirculation is altered in the postprandial phase in patients with type 2 diabetes, and the correction of the metabolic control could improve it (37).

From a nutritional standpoint, the mixed meal used in this study had a relatively high carbohydrate content. Because the IR-associated hemodynamic disturbances occurred concomitantly with a glucose peak and hyperinsulinemia (Figure 4), it was tempting to speculate that a low-carbohydrate or a low–glycemic index diet might have differently interfered with the vascular system and modulated detrimental postmeal alterations. This hypothesis needs to be tested in future studies.

Variations of hemodynamic variables more intrinsically related to cardiac function (eg, IVRT and LVET) showed no significant differences in fasting and postprandial phases in IR compared with in IS subjects. In the Offspring Framingham Heart Study, hyperglycemia and insulin resistance were linked to diastolic dysfunction and cardiac structure, as assessed by magnetic resonance (38), but participants were much older (aged 64 ± 9 y).
and more hyperglycemic than were the subjects in the current study, in whom cardiac abnormalities should not have been present. This reinforced the hypothesis that main hemodynamic disturbances of insulin resistance are located in the peripheral and splanchnic vasculature, at least in the earliest phase, rather than at the cardiac level.

We recognized that this study had some limitations. First, the ICG for noninvasive monitoring of cardiac variables has sometimes given conflicting results in terms of reliability (39–41). Nonetheless, we decided to use the ICG because it allowed the noninvasive and continuous recording of emodynamic variables, which were otherwise unrealistic with more precise but invasive techniques. Another limitation was related to the age and sex imbalance between IR and IS subjects. However, with adjustment of statistical analyses for age and sex, we showed that our findings were not confounded by these characteristics. Moreover, no differences between sexes have been described in postprandial splanchnic-flow variables (42).

Although the vascular actions of insulin are well-recognized, the importance of this study relied on the identification of an altered metabolic and vascular coupling in young healthy subjects with mild insulin resistance. It should be emphasized that our study subjects showed hemodynamic alterations despite relatively mild metabolic impairment. Therefore, this observation stressed the concept that the negative relation between metabolic and vascular impairment starts early during the clinical course of insulin-resistance syndromes and may be prevented by a nutritional intervention.

In conclusion, in this cross-sectional study, we show that nondiabetic IR subjects had increased fasting vascular resistances and a shorter duration of vasodilatation after a meal, whereas cardiac-function variables appeared normal. These early hemodynamic alterations may be important in the pathogenesis of cardiovascular disease in IR subjects.

The authors’ responsibilities were as follows—SVdK: conducted research and wrote the manuscript; GPF: performed statistical analyses and wrote the manuscript; FB, ER, and GC: conducted research and revised the manuscript; MB: contributed to the interpretation of data and revised the manuscript; CC and MB: contributed to the interpretation of data and revised the manuscript; AA: contributed to the study design and provided critical revision of the manuscript; and all authors: had full access to all data in the study and took responsibility for the integrity of the data and accuracy of data analyses. None of the authors declared a personal or financial interest associated with this manuscript.

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