Effects of Different Insulin Regimes on Postprandial Myocardial Perfusion Defects in Type 2 Diabetic Patients

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OBJECTIVE — Postprandial glycemia is an independent risk factor for cardiovascular disease that is more powerful than fasting glycemia and determines myocardial perfusion defects in type 2 diabetes. We examined the efficacy of two different insulin regimes (regular insulin and insulin analog) in controlling postprandial hyperglycemia and in preventing myocardial perfusion abnormalities.

RESEARCH DESIGN AND METHODS — A total of 20 consecutive type 2 diabetic patients and 20 control subjects were enrolled in this randomized, three-way, cross-over, placebo-controlled study. Myocardial perfusion was assessed by myocardial contrast echocardiography (MCE) in fasting and postprandial (120 min) state.

RESULTS — Insulin analog was associated with lower, but not statistically significant, postprandial glycemia than regular insulin (glucose increase: 116 ± 8 vs. 136 ± 5%, P = NS). However, the area under the curve following insulin analog was significantly lower than regular insulin (18,354 ± 702 vs. 20,757 ± 738 mg per 120 min, P = 0.032). Fasting myocardial flow velocity (MBF), myocardial blood volume (MBV), and myocardial blood flow (MBF) did not differ between control and type 2 diabetic subjects. Postprandial MBF (0.67 ± 0.24 vs. 0.92 ± 0.25, P < 0.01), MBV (8.4 ± 2 vs. 10.9 ± 1.2, P < 0.01), and MBF (5.6 ± 2 vs. 9.9 ± 2.8, P < 0.01) increased significantly in control subjects. In type 2 diabetes, during placebo in the postprandial state, MBF increased (0.65 ± 0.27 vs. 0.89 ± 0.24, P < 0.01), while MBV (8.34 ± 1.2 vs. 4.3 ± 1.3, P < 0.01) and MBF (5.4 ± 1.5 vs. 3.4 ± 0.9, P < 0.01) decreased. Similar changes in MCE variables were observed after regular insulin: MBF increased (0.65 ± 0.22 vs. 0.92 ± 0.12, P < 0.01) and MBV (8.2 ± 2 vs. 5.2 ± 1.16, P < 0.01) and MBF (5.4 ± 1.9 vs. 4.2 ± 0.86, P < 0.01) were reduced. After insulin analog, postprandial MBF (0.66 ± 0.18 vs. 0.9 ± 0.18, P < 0.01), MBV (8.2 ± 1.6 vs. 9.6 ± 1.2, P < 0.01), and MBF (5.4 ± 2 vs. 7.2 ± 1.9, P < 0.01) increased. Values of postprandial MBV and MBF were higher after insulin analog than regular insulin treatment.

CONCLUSIONS — Insulin analog partially reversed myocardial perfusion abnormalities observed in postprandial state by improving glucose control.

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Abbreviations: AUC, area under the curve; CVD, cardiovascular disease; FFA, free fatty acid; MBF, myocardial blood flow; MBV, myocardial blood volume; MCE, myocardial contrast echocardiography.

A table elsewhere in this issue shows conventional and Systeme International (SI) units and conversion factors for many substances.

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Insulin and postprandial myocardial perfusion defects

Table 1—Study population characteristics at baseline, in fasting state

<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects</th>
<th>Diabetic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46 ± 8</td>
<td>48 ± 5</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>12/8</td>
<td>12/8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4 ± 1.4</td>
<td>27.6 ± 1.2</td>
</tr>
<tr>
<td>Glucose (md/dl)</td>
<td>87 ± 11</td>
<td>146 ± 27*</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>4.5 ± 0.4</td>
<td>7.2 ± 1*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>175 ± 15</td>
<td>222 ± 38</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>62 ± 13</td>
<td>52 ± 11*</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>112 ± 58</td>
<td>130 ± 71*</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>89 ± 19</td>
<td>147 ± 42*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>70 ± 9</td>
<td>68 ± 6</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>115 ± 8</td>
<td>116 ± 9</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>70 ± 5</td>
<td>74 ± 6</td>
</tr>
</tbody>
</table>

Data are means ± SD. *P < 0.01 compared with nondiabetic control subjects.

Study design

This study was conducted according to a randomized, three-way, cross-over design. There were 3 study days (separated by a 5- to 10-day interval). Patients were on their own diet regimen, and no medication for glycemic control was used between visits. During these 3 study days, the following three therapeutic regimens were adopted in a random order: 1) regular insulin (Actrapid; Novo Nordisk, Bagsvaerd, Denmark) injected subcutaneously in the perumbrellal region 25 min before the standard meal, 2) insulin analog (Novorapid; Novo Nordisk) injected subcutaneously in the perumbrellal region immediately before the standard meal, and 3) saline (placebo) injected subcutaneously. Both physicians and patients were blinded to active medications. Blood samples were drawn for obtaining fasting plasma glucose, free fatty acids (FFAs), insulin, and lipid levels.

Diabetic patients and control subjects assumed a mixed standardized meal (460 kcal; 54% carbohydrates, 31% lipids, and 25% proteins) (Novasource Novartis). The meals were consumed over a 5-min period under supervision of a nurse. Myocardial perfusion by contrast echocardiography was performed before and 2 h after eating.

Myocardial contrast echocardiography

Myocardial contrast echocardiography (MCE) was performed in apical four- and two-chamber views using intermittent harmonic imaging with a phased-array system (Sonos 5500) interfaced to a S3 transducer that transmits ultrasound at a mean frequency of 1.6 MHz and receives it at 3.2 MHz. The transmit power was set at maximum, and compression was set at 50 dB. Mechanical index was 1.4. Gain settings were optimized at the beginning of each study and were subsequently held constant. Continuous venous infusion of a contrast agent (Levovist; Schering, Berlin, Germany) was performed using an infusion pump (Medrad Pulsar, Indianola, IA). An intensity versus dose curve from the left ventricular cavity was plotted to obtain the dose where the relation was linear. This dose was used in the contrast echocardiographic studies. In each patient, to avoid significant changes in the concentration of contrast in left ventricular cavity before and after the meal only studies with similar values of peak left ventricular cavity contrast intensity (contrast intensity) were analyzed. We accepted a range in peak contrast intensityfasting-to-peak contrast intensitypostprandial ratio from 0.9 to 1.1. Absence of any change in myocardial video intensity over five successive frames by visual assessment indicated the steady state. Once steady state was achieved, repeat imaging was obtained using sequential electrocardiogram triggering at end-systole. The pulsing interval was gated to the electrocardiogram and progressively increased from 80 msec to 10 s. Up to 12 images, acquired at each pulsing interval, were recorded on optical disk for quantitative analysis. Background-subtracted myocardial signal intensity was plotted over the increasing pulsing intervals and fit to an exponential function as described by Wei et al. (9) for the determination of the slope of the ascending curve of myocardial contrast intensity (β), which provides a measure of myocardial flow velocity, and the myocardial plateau intensity, which correlates to capillary cross-sectional area and hence to myocardial blood volume (MBV). The product (β × MBV) represents a dimensionless index of myocardial blood flow (MBF). Digitized studies were coded and read by two independent observers blinded to the patient’s identity and the order of the study. An index of mean global myocardial perfusion was calculated by adding the values of regional MBF and dividing this value by the number of analyzed left ventricular segments. In 10 control and 10 diabetic patients in fasting state, repeated measurements for MBV or β were done to calculate the inter- and intraobserver variability. For this reason we used Pearson’s linear correlations. In this study, the degree of inter- and intraobserver correlations for measurements of MBV (correlation coefficient r = 0.94, linear regression line equation y = 0.852x + 1.03, SD of residuals from the line SD = 0.21 and r = 0.96, y = 0.867x + 1.02, SD = 0.20, respectively) and β (r = 0.94, y = 0.86x + 0.072, SD = 0.023 and r = 0.95, y = 0.88x + 0.071, SD = 0.021, respectively) was acceptable.

Analytical methods

Plasma glucose was measured with the glucose oxidase method on a Beckman Glucose Analyser. Analyses of area under the curve (AUC) was performed by using the trapezoid rule. The total FFA concen-
tration was determined with a microenzy-
matic technique (coefficient of variation
= 6.9 ± 2.3%). Plasma insulin and C-
peptide were measured by conventional
radioimmunoassay (coefficient of varia-
tion = 6 ± 4 and 5.3 ± 3.2%, respectively).
Total plasma cholesterol was measured
enzymatically with a within-
batch precision of 1.57% and a between-
batch precision of 2.09%. HDL
cholesterol was assayed according to the
method of Kostner with a within-batch
precision of 1.55% and a between-batch
precision of 4.1%. LDL cholesterol was
determined with the Friedewald formula:

\[
LDL = \text{total cholesterol} - \text{HDL cholesterol} - \text{triglycerides}/5
\]

Triglycerides were assayed by a commercially available kit
based on enzymatic method; intra-assay
precision was 2.23% and interassay pre-
cision 2.78%. A1C was assayed with a
chromatographic method.

Statistical analysis
Results are expressed as means ± SD for
normally distributed variables. Compari-
son between fasting and postprandial val-
ues and between groups were made with
the Student's t test (paired and unpaired
as appropriate). Multiple comparisons
were performed with repeated-measure
ANOVA, followed by the Fisher protected
least significant difference test. Frequen-
cies of a postprandial plasma glucose level
≤120 mg/dl during regular insulin or in-
sulin analog regimen were compared with
the \(X^2\) test. For all statistical analysis we
used the SPSS package version 10.1 for
Windows (SPSS, Chicago, IL). A P value
≤0.05 by the two-tailed test was consid-
ered to indicate a statistical significance.

RESULTS
Hemodynamic variables, serum
glucose, lipids, FFAs, and insulin
Heart rate and systolic and diastolic blood
pressure in fasting state did not differ be-
tween diabetic patients and control sub-
jects. Two hours after eating, heart rate
and systolic and diastolic blood pressure
did not change significantly in either treat-
ment group of diabetic patients (regu-
lar insulin, insulin analog, or placebo) or
in control subjects. Hence, in type 2 dia-
abetic patients, fasting rate-pressure prod-
uct was similar to postprandial value
independent of experimental conditions
(placebo 8,050 ± 1,596, regular insulin
8,020 ± 1,650, insulin analog 8,065 ±
1,674; \(P = \text{NS for all comparison}\)). In fast-
ing state, type 2 diabetic patients showed
higher plasma glucose concentration than
control subjects. Moreover, total chole-
sterol, LDL cholesterol, and triglyceride
levels were higher, while HDL cholesterol
levels were lower in diabetic patients than
in control sub-
jects (Table 1).

In the placebo study, the postprandial
plasma glucose concentrations in type 2 dia-
abetic patients were significantly higher than
those in control subjects (223 ± 11 vs.
124 ± 18 mg/dl, \(P < 0.002\)). In the stud-
ies in which regular insulin or insulin an-
alog were injected, postprandial plasma
blood glucose increased significantly from base-
line values, but the peak values were sig-
ificantly lower than those observed
during the placebo study. Percentage
changes in glucose values during insulin
analog were not statistically different from
those observed following regular insulin
(116 ± 8 vs. 136 ± 5%, \(P = \text{NS}\)) (Fig. 1).
However, the value of AUC for glucose after regular insulin (20.757 ± 738 mg·dl⁻¹·120 min⁻¹) was significantly higher than that observed following insulin analog (18.354 ± 702 mg·dl⁻¹·120 min⁻¹, P = 0.032) (Fig. 2). Furthermore, a postprandial plasma glucose concentration ≤120 mg/dl was obtained in 12 of 20 (60%) diabetic patients during insulin analog treatment but in only 6 of 20 (30%) patients during regular insulin regimen (P < 0.01). No significant changes were observed between control subjects and type 2 diabetic patients in insulin levels, FFAs, or triglyceride profiles at any study point (Fig. 1).

Myocardial perfusion

MCE studies showed that fasting β, MBV, and MBF did not differ between control subjects and type 2 diabetic patients in the three treatment groups (Table 2). Changes in MBV expression of the capillary cross-sectional area following the mixed meal are shown in Fig. 3. In the postprandial state, β (0.67 ± 0.24 vs. 0.92 ± 0.25, P < 0.01) and MBV (8.4 ± 2.0 vs. 10.9 ± 1.2, P < 0.01) increased significantly from fasting values in control subjects. As a consequence, postprandial MBF also increased in nondiabetic subjects (5.6 ± 2.0 vs. 9.9 ± 2.8, P < 0.01).

In type 2 diabetic patients, during placebo in the postprandial state, β increased (0.65 ± 0.27 vs. 0.89 ± 0.24, P < 0.01), while MBV (8.34 ± 1.2 vs. 4.3 ± 1.3, P < 0.01) and MBF (5.4 ± 1.5 vs. 3.4 ± 0.9, P < 0.01) reduced significantly in comparison to fasting values. This pattern of postprandial changes in MCE variables did not change significantly after injection of regular insulin before the meal: postprandial β increased (0.65 ± 0.22 vs. 0.9 ± 0.12, P < 0.01) but MBV (8.2 ± 2 vs. 5.2 ± 1.16, P < 0.01) and MBF (5.4 ± 1.9 vs. 4.2 ± 0.86, P < 0.01) decreased significantly. In type 2 diabetic patients, in whom insulin analog was injected before eating, all MCE variables increased significantly in comparison to fasting values: β from 0.66 ± 0.18 to 0.9 ± 0.18 (P < 0.01), MBV from 8.2 ± 1.6 to 9.6 ± 1.2 (P < 0.01), and MBF from 5.4 ± 2 to 7.2 ± 1.9 (P < 0.01). Comparisons between type 2 diabetic patients and control subjects show that postprandial β does not differ, while postprandial MBV and MBF are lower irrespective of treatment.

Comparisons between diabetic patients treated with placebo or with different insulin regimens show that the highest postprandial MBV and MBF are obtained after insulin analog injection. Values of postprandial MBV and MBF are higher in diabetic patients after regular insulin injection than those of patients treated with placebo.

CONCLUSIONS — This study demonstrated that insulin analog rather than regular insulin, when administered to type 2 diabetic patients in a controlled mixed meal test setting, improved postprandial glycemic control and has the potential to partially reverse myocardial perfusion abnormalities observed in this metabolic state. In type 2 diabetic patients, a significant decrease in myocardial perfusion, which correlated with hyperglycemia during the postprandial state, has been recently demonstrated (7). This postprandial reduction in myocardial perfusion was determined by a deterioration in function of coronary microvascular circulation as demonstrated by the reduction in myocardial blood volume assessed by MCE. This parameter is related to microvascular indexes (total microvascular density, capillary density, and capillary area) in biopsied myocardial segments (10). The present study confirmed that myocardial perfusion defects due to a microvascular coronary dysfunction occur in the postprandial state in type 2 diabetic patients treated with diet. Similar postprandial myocardial perfusion defects occurred in patients in whom regular insulin was injected but were prevented, together with a better glycemic control, by the injection of insulin analog before the meal.

The occurrence and reversion of myocardial perfusion defects in the postprandial state may recognize a multifactorial pathogenesis. Information from in vitro and in vivo studies have provided biochemical mechanisms by which in-
In addition to this vasoactive action in the muscle, it has been shown that insulin induces vasodilation and increases perfusion by a rapid capillary recruitment that stimulates a dose-dependent production of nitric oxide–dependent vasodilatory stimuli (11–13). Besides the production of free radical species, hyperglycemia activates the polyol and glucosamine pathways, increases advanced glycation end product synthesis, and activates protein kinase C (14). A better control of hyperglycemia may reverse this complex metabolic derangement. Moreover, in addition to this action on myocardial substrate metabolism, insulin has a physiological role in vasodilating arterial (15) and venous (16) beds through an increase in nitric oxide synthesis and release. It has been also shown that insulin induces a dose-dependent expression of endothelial nitric oxide synthase in human aortic endothelial cells (17) and stimulates a dose-dependent production of nitric oxide in human umbilical vein endothelial cell (18). Moreover, in human skeletal muscle, it has been shown that insulin induces vasodilation and increases perfusion by a rapid capillary recruitment that is blunted in insulin-resistant states (19).

Insulin may reverse the compensatory increase in plasma glucose levels of 20 mg/dl observed in admission plasma glucose levels in patients with acute myocardial infarction (22). Postprandial glucose peak (4,23,24) is an independent risk factor, especially with respect to CVD. Prevention and delay of late diabetes complications has been shown to be dependent on glycemic control as measured by level of A1C (2,3). The Diabetes Control and Complications Trial (2) showed that at equivalent levels of A1C, patients on intensive basal-bolus therapy had a reduced risk of complications compared with patients on conventional insulin therapy. This may imply that features of glycemic control not reflected by A1C such as postprandial glycemia may add to or modify the risk of complications. The glycemic control in type 2 diabetic patients occurred only if postprandial glucose control is part of the therapeutic regimen (25), as convincingly shown by Bastyr et al. (26) in the IOEZ study group, in which insulin lispro was used to focus on postprandial blood glucose, resulting in greater impact on overall metabolic control. These observations suggest that control of excessive postprandial glycemia may give clinical benefits in type 2 diabetic patients.

Postprandial abnormalities in myocardial perfusion have been related to peak glucose values (7). In the present study, although insulin analog treatment was associated with peak glucose values not statistically different from those observed following regular insulin, it provided a significant amelioration of postprandial plasma glucose (as indicated by the AUCs) without substantial differences in insulin concentrations. Moreover, a postprandial plasma glucose concentration ≤120 mg/dl was obtained in 60% of diabetic patients during insulin analog treatment but only in 30% of patients during regular insulin regimen.

It should be noted that the small differences in plasma glucose levels may lead to significant changes in vascular response to insulin. This hypothesis stems from the observations made by Capes et al. (27) who showed that small difference in admission plasma glucose levels in patients with acute myocardial infarction but without previously known diabetes are associated with tremendously different outcomes. Furthermore, differences in plasma glucose levels of 20 mg/dl are associated with a twofold increase in cardiogenic shock in patients with acute myocardial infarction (28).

In conclusion, myocardial perfusion defects induced by postprandial hyperglycemia may have relevant clinical implications because, as suggested by the response-to-injury hypothesis (29), they represent an early marker of atherogenic process in the coronary circulation, and their recognition may offer new hope for the early identification of subgroups of patients at increased risk of coronary vessels obstructive disease. Moreover, it may constitute an important goal in the treatment of the disease. The present study offers a practical clinical approach to this relevant problem showing that treatment with insulin analog immediately before eating, by allowing better postprandial glycemic control, either attenuates or reverses the myocardial perfusion defects and coronary microvascular dysfunction in the postprandial state.
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References


6. Ceriello A: Postprandial hyperglycemia and diabetes complications: is it time to treat (Review)? *Diabetes* 54:1–7, 2005


