Myocardial Infarction Before the Age of 40 Years Is Associated With Insulin Resistance

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Insulin resistance is associated with atherosclerosis, and hyperinsulinemia is predictive of coronary heart disease. However, a quantitative estimation of in vivo insulin sensitivity in juvenile myocardial infarction is still lacking and the mechanism of hyperinsulinemia is unknown. We estimated insulin sensitivity, β-cell secretion, and hepatic insulin extraction using the minimal model analysis of a frequently sampled intravenous glucose tolerance test (FSIGT) in 25 normal-weight subjects without glucose intolerance and hypertension who had an acute myocardial infarction before the age of 40 years, and 10 control subjects comparable for age, sex, body mass index, and blood pressure. All patients underwent a coronary angiography. Insulin sensitivity was significantly lower in patients than in control subjects (mean ± SEM, 4.6 ± 0.6 *v* $8.5 \pm 1.2\ 10^{-4} \cdot min^{-1}/(\mu U/mL)$, $P = .002$). The basal C-peptide secretion rate ($P = .02$), total C-peptide secretion ($P = .005$), area under the curve (AUC) of insulin ($P = .04$) and C-peptide ($P = .01$), and hepatic insulin extraction ($P = .04$) were higher in patients versus control subjects. In conclusion, insulin resistance is evident in subjects with early myocardial infarction accurately selected to avoid the influence of other factors known to reduce insulin sensitivity, and hyperinsulinemia is due to an increase in β-cell secretion rather than a decrease in hepatic insulin extraction.

INSULIN RESISTANCE is associated with an increased prevalence of conventional cardiovascular risk factors such as hypertension, dyslipidemia, an android pattern of body fat distribution, and impaired glucose tolerance or diabetes.[1] Large-scale epidemiologic studies have indicated that hyperinsulinemia is a predictor of coronary heart disease in both nondiabetic and diabetic subjects.[2,3] Fasting hyperinsulinemia and/or a hyperinsulinemic response to a glucose challenge have been reported in subjects with overt coronary heart disease,[4,5] and a positive association between plasma insulin levels and angiographically documented significant coronary artery disease has been found.[6] Further, a link between insulin resistance and atherosclerosis[7-9] has been shown by measuring insulin sensitivity.

However, insulin resistance in patients with myocardial infarction before the age of 40 years has never been evaluated. The interest of this issue is related to the particular characteristics of patients with cardiovascular events early in life. There is a high frequency of coronary arteries that are angiographically normal or affected by single-vessel disease.[10-13] Smoking is particularly frequent,[10,12-15] but conflicting results have been reported for the prevalence of other conventional cardiovascular risk factors.[12,16] In this respect, the relevance of the association between insulin resistance and early myocardial infarction is still lacking. In particular, insulin sensitivity has never been measured in vivo and the mechanisms responsible for hyperinsulinemia have never been elucidated.

The purpose of this study is to provide a quantitative estimation of insulin sensitivity, β-cell secretion, and hepatic insulin extraction in a group of patients who had an acute myocardial infarction before the age of 40 years. Patients with coronary artery disease show several abnormalities known to influence insulin sensitivity such as obesity, hypertension, glucose intolerance, or chronic heart failure. Therefore, patients were strictly selected to avoid the influence of these confounding factors. We aimed to detect whether the presence of insulin resistance is independently associated with myocardial infarction at a young age.

SUBJECTS AND METHODS

Subjects

From 98 consecutive patients aged less than 40 years who survived a first episode of acute myocardial infarction, 25 subjects were selected using the following criteria: a negative personal or familial history of diabetes or hypertension, non-obese, nonhypertensive, normal glucose tolerance, and normal left ventricular function.

Myocardial infarction was diagnosed according to the criteria of the World Health Organization.[17] A coronary angiography was performed by the Judkins or Sones technique, and multiple views of the right and left coronary arteries were recorded on 35-mm cine film. The severity of coronary artery disease was quantified according to the Gensini scoring system.[18] The most severe stenosis in each of 10 segments was graded according to severity as follows: less than 25% stenosis of the luminal diameter, 0; 25% to 49% stenosis, 1; 50% to 74% stenosis, 2; 75% to 89% stenosis, 4; 90% to 98% stenosis, 8; 99% stenosis, 16; and total occlusion, 32. The points for each of the 10 segments were summed and a coronary atherosclerosis score was obtained. The angiographer was blind to the clinical characteristics or metabolic variables of the patients.

Ten healthy subjects with normal glucose tolerance and a negative family history for diabetes or hypertension were chosen to obtain a control group comparable for age, sex, body mass index, and blood pressure. In patients and controls alike, there was no recent change in body weight, intercurrent illness, or use of medication. All patients were treated by a combination of low-dose β-blocking agent and angiotensin-converting enzyme (ACE) inhibitor. Dietary assessment by a trained dietitian indicated that all subjects ate a balanced (45% carbohydrate, 25% protein, and 30% fat) and stable diet of 125 to 145 kJ/kg/d, containing less than 50 g ethanol and a minimum of 150 g

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carbohydrate per day. Physical activity estimated by a questionnaire[19] was comparable in the two groups (mean ± SEM, 11,813 ± 523 *v* 12,237 ± 513 kJ/d, patients *v* controls). Among the control subjects, we chose the more sedentary individuals to obtain a group comparable to the patients. All subjects were instructed to refrain from intense physical exercise on the day preceding the study. Subjects were classified as smokers if they smoked currently or within the previous 10 years. A mercury sphygmomanometer was used to obtain 3 values for systolic and diastolic blood pressure after a 15-minute rest period: the average of the 3 values was used for data analyses. All procedures were in accordance with the Helsinki Declaration of 1975. Informed consent was obtained from all subjects.

Tests

All patients and control subjects underwent an oral glucose tolerance test (OGTT) and, after 7 to 10 days, a frequently sampled intravenous glucose tolerance test (FSIGT). The patients were studied at least 3 months (median, 123 days; range, 114 to 131) after the acute event. Medications known to affect insulin sensitivity were discontinued in the last 4 days before each test.

The OGTT was performed and interpreted according to World Health Organization criteria.[20] The FSIGT started between 8:00 and 8:30 AM after an overnight fast. A butterfly needle was inserted into an antecubital vein, and patency was maintained with a slow saline drip. After a 20-minute rest period, basal blood samples were drawn at −8 and −3 minutes, after which glucose (0.33 g/kg body weight) was injected over 1 minute starting at time 0. Additional samples were obtained from a contralateral antecubital vein at times 2, 3, 4, 5, 6, 8, 10, 13, 16, 20, 25, 30, 40, 60, 80, 100, 120, 150, 180, and 240 minutes. Samples were rapidly collected via a 3-way stopcock connected to the butterfly needle. Venous blood samples for lipids and apolipoproteins were obtained after an overnight fast, collected in a vacutainer tube containing EDTA, and centrifuged for 30 minutes at 2,500 rpm at 4°C in a J6B centrifuge (Beckman, Palo Alto, CA). Plasma was stored at −20°C until processed.

Assays

The serum glucose level was measured in duplicate by the glucose oxidase method (Glucose Analyzer II; Beckman Instruments, Fullerton, CA). The coefficient of variation was ±1.6%. The serum insulin level was measured in duplicate by solid-phase antibody radioimmunoassay (Corning, Medfield, MA), and the serum C-peptide level was measured in duplicate by radioimmunoassay (Byk-Mallinkrodt, Dietzenbach, Germany). The between- and within-assay coefficients of variation for insulin and C-peptide were 9% and 6% and 11% and 8%, respectively.

Total cholesterol and triglyceride levels were measured enzymatically. High-density lipoprotein (HDL) cholesterol was determined after precipitation of apolipoprotein B (apoB)-containing lipoproteins with heparin and manganese chloride.[21] Low-density lipoprotein (LDL) cholesterol was calculated according to the method of Friedewald et al.[22] Plasma apoB and apoA1 were determined by the turbidimetric method (Poli Diagnostici, Milan, Italy).

Data Analysis

Data from the FSIGT were analyzed by exploiting the mathematic models that describe the time course of glucose, insulin, and C-peptide concentrations. The minimal model of glucose disappearance,[23] by accounting for the effect of insulin and glucose on glucose disappearance, provides two parameters: S_I, the insulin sensitivity index ($\times 10^{-4}$ per minute per microunit per milliliter), and S_G, glucose effectiveness (per minute). The model of insulin secretion and kinetics[24] describes the effect of glucose on C-peptide secretion and the kinetics of C-peptide and insulin after their entry into the peripheral circulation. This model provides the time course of C-peptide secretion [CPS(t)] and posthepatic insulin delivery [IDR(t)] in addition to the following parameters: Φ_1, the dynamic (suprabasal) first-phase β-cell (prehepatic) sensitivity to glucose (picomolars per minute per milligram per deciliter); Φ_2, the sensitivity of the second phase (picomolars per minute per milligram per deciliter); and k_{01}, the C-peptide fractional clearance rate (per minute), ie, the disappearance rate in unit time per unit volume. Because insulin and C-peptide are secreted in equimolar fashion, CPS(t) also represents the time course of β-cell (prehepatic) insulin secretion. Therefore, the time course of the percent hepatic insulin extraction may be computed as the difference between CPS(t) and IDR(t), normalized to CPS(t).

Calculations

The intravenous tolerance factor K_G was calculated as the slope of the logarithm of glucose concentration versus time at the samples at 13, 16, 20, 25, 30, and 40 minutes after the injection. The integral over 240 minutes of CPS(t) yields TIS (picomoles in 240 minutes), ie, the total amount of insulin release per unit volume (liter) by the β cell.[24] The method also allows the calculation of basal prehepatic C-peptide and insulin production per unit volume ([BSR] picomoles per minute).[24] The mean hepatic insulin extraction (Hm) is computed as the integral of the insulin extraction time course divided by the length of the test (240 minutes). The total area under the concentration curve (AUC) was calculated by integration with the trapezoidal rule. The estimation of model parameters was performed by the MINMOD program,[25] which was adapted to also include the C-peptide model.[24] All values are expressed as the mean ± SEM. Statistical analysis was performed using Student's *t* test and χ^2 test.

RESULTS

Clinical and metabolic characteristics of the two groups of subjects are reported in Table 1. HDL cholesterol ($P = .03$) and apoA1 lipoprotein ($P = .04$) were significantly lower in patients than in control subjects, whereas plasma apoB lipoprotein

Table 1. Clinical Characteristics of the Patients and Control Subjects

Characteristic	Control Subjects	Patients
No. of subjects	10	25
Age (yr)	36 ± 1	35 ± 1
Sex ratio (male/female)	8/2	23/2
Smoker before MI, (yes/no)	2/8	19/6*
BMI (kg/m^2)	24.5 ± 0.9	25.6 ± 0.6
WHR	0.89 ± 0.01	0.92 ± 0.01
Triglycerides (mmol/L)	1.2 ± 0.9	1.7 ± 0.5
Total cholesterol (mmol/L)	4.8 ± 0.2	5.2 ± 0.2
LDL cholesterol (mmol/L)	2.7 ± 0.2	3.3 ± 0.2
HDL cholesterol (mmol/L)	1.5 ± 0.1	1.2 ± 0.1†
ApoA1 (mmol/L)	3.4 ± 0.3	2.8 ± 0.1‡
ApoB (mmol/L)	2.1 ± 0.1	2.7 ± 0.1§
Fasting serum glucose (mmol/L)	4.5 ± 0.1	4.9 ± 0.1
Fasting serum insulin (pmol/L)	54.1 ± 6.3	69.2 ± 7.8
Fasting serum C-pepitde (nmol/L)	0.54 ± 0.04	0.72 ± 0.06
Systolic blood pressure (mm Hg)	126 ± 4	124 ± 2
Diastolic blood pressure (mm Hg)	79 ± 2	80 ± 2

NOTE. Results are the mean ± SEM.

Abbreviations: MI, myocardial infarction; BMI, body mass index; WHR, waist to hip ratio.

*$P = .002$, χ^2 test.

†$P = .03$, ‡$P = .04$, §$P = .02$: Student's *t* test.

levels ($P = .02$) were significantly higher in patients versus controls. Smokers were more frequent in patients than in control subjects ($P = .002$). Fasting serum insulin and C-peptide levels were slightly but not significantly higher in patients versus control, whereas fasting serum glucose values were similar in the two groups.

The scores for coronary artery lesions are reported in Table 2. The analysis of angiograms showed that 28% of the patients had angiographically normal coronary arteries (score 0) and none showed a stenosis of 76% or higher in any segment.

The time course of serum glucose, insulin, and C-peptide levels in the two groups during the FSIGT are shown in Fig 1, and the metabolic parameters are reported in Table 3. S_I was significantly lower ($P = .002$) in patients than in control subjects (Fig 2), whereas S_G was similar in the two groups. In the patients, BSR ($P = .02$) and TIS ($P = .005$) were 2-fold higher than in control subjects, whereas $\Phi 1$, $\Phi 2$, and K_G were not significantly different in the two groups. Insulin and C-peptide AUC were significantly higher in patients versus control subjects ($P = .04$ and $P = .01$, respectively). Hm was significantly higher in the patients ($P = .04$). No significant correlation was found between S_I and the coronary artery score or plasma lipids.

DISCUSSION

Insulin sensitivity was significantly lower in patients than in control subjects (Fig 2), and this reduction was relevant (about 45%). Insulin resistance in early myocardial infarction has been previously suggested only on the basis of fasting plasma glucose and insulin concentrations.[26,27] The present study provides the first evidence of insulin resistance in patients with early myocardial infarction assessed under dynamic conditions together with a quantitative evaluation of several other metabolic parameters related to glucose disappearance and insulin secretion and clearance. The validity of this result depends on how other factors that can reduce insulin sensitivity may be excluded. Our patients were strictly selected to avoid the influence of age, obesity, hypertension, glucose intolerance, chronic heart failure, and medications known to induce insulin resistance. The β-blocking agents and ACE inhibitors have opposite effects on insulin sensitivity. Since these agents were used in low doses and were discontinued in the last 4 days before the tests, any interference on insulin sensitivity may be reasonably excluded. Further, an excess of visceral adipose tissue may contribute to insulin resistance.[28] Although abdominal adiposity as estimated by the waist to hip ratio was similar in the two groups, an increase of visceral adipose tissue in the patients cannot be excluded. Smoking may reduce insulin sensitivity,[29,30] and in our study the proportion of smokers is higher in patients versus control subjects (Table 1). Indeed, all smoking patients are ex-smokers, since they quit at the time of acute myocardial infarction. For these reasons, the defective insulin action on glucose metabolism can be considered independent of other confounding factors.

For the current investigation, we used the minimal model method.[23,31] This was used mainly due to its equivalence for the assessment of overall insulin sensitivity and low invasiveness compared with the clamp technique,[32] and because it is able to provide a simultaneous picture of the time course of the

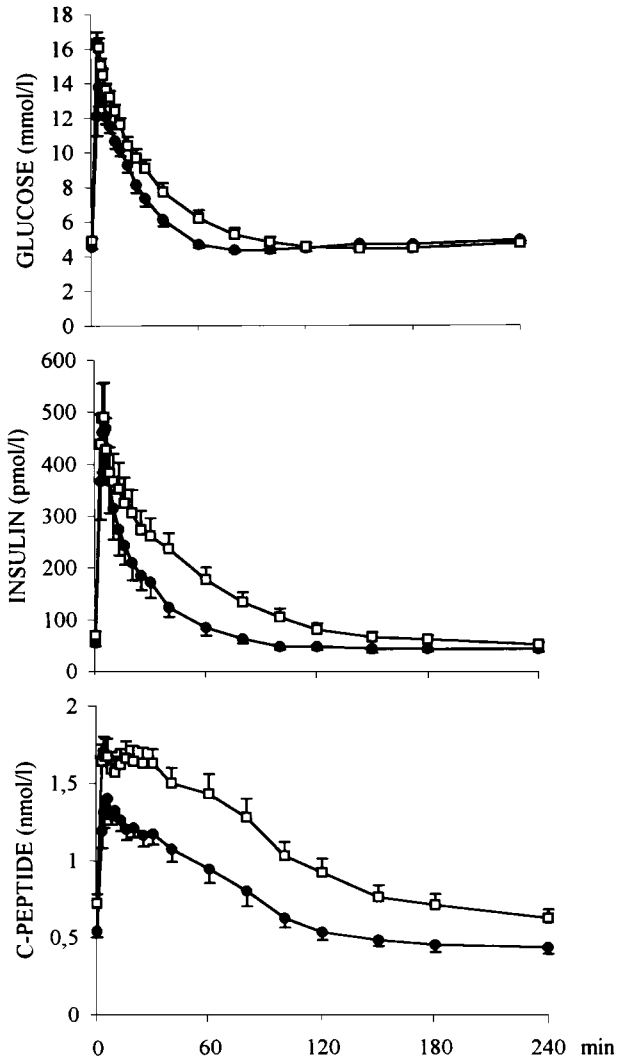

Fig 1. Time course of serum glucose, insulin, and C-peptide during the FSIGT in 25 patients with early myocardial infarction (□) and 10 control subjects (●). Glucose (0.33 g/kg body weight) was injected at time 0. Results are the mean ± SEM.

Table 2. Coronary Artery Score in 25 Patients With Early Myocardial Infarction

	Patients	
Score	No.	%
0	7	28
1	2	8
3	3	12
4	3	12
5	2	8
6	3	12
7	2	8
8	2	8
12	1	4
Total	25	100

Table 3. Model-Derived Metabolic Parameters of Glucose Disappearance and β-Cell Secretion in Patients With Juvenile Myocardial Infarction and Control Subject

Parameter	Control Subjects	Patients
Glucose disappearance		
K_G	2.16 ± 0.14	1.87 ± 0.18
S_I (10^{-4} · min^{-1}/(μU/mL))	8.52 ± 1.20	4.61 ± 0.58*
S_G (min^{-1})	0.03 ± 0.01	0.02 ± 0.01
Insulin secretion		
C-peptide AUC (nmol/L/240 min)	169 ± 11	250 ± 20†
k_{01} (min−1)	0.07 ± 0.01	0.07 ± 0.01
Φ1 (pmol/L · min^{-1} · mg^{-1} · dL)	103 ± 13	87 ± 9
Φ_2(pmol/L · min^{-2} · mg^{-1} · dL)	0.04 ± 0.01	0.05 ± 0.01
TIS (pmol/L)	10,787 ± 1,088	19,362 ± 1,759‡
BSR (pmol/L/min)	26.8 ± 2.4	47.2 ± 5.1§
Hm (%)	75.8 ± 4.4	83.4 ± 1.5‖
Insulin AUC (pmol/L in 240 min)	20.1 ± 2.4	31.2 ± 3.2¶

NOTE. Data are the mean ± SEM analyzed by Student's *t* test.
*P = .002.
†P = .01.
‡P = .005.
§P = .02.
‖P = .04.
¶P = .04.

β-cell and liver processes involving insulin under dynamic conditions, without calculating the C-peptide to insulin molar ratio, the validity of which is limited to steady-state conditions, given the different kinetics of the two peptides.[33] It should be emphasized that the FSIGT was performed without additional injection of tolbutamide or insulin, as previously suggested to increase the dynamics of the test and thus improve the accuracy of the estimates.[23] Exogenous administration of secretagogues or insulin was avoided to study pancreatic function without any other confounding factor. In addition, it has been shown that S_I is the same in the different protocols,[34] providing there is sufficient insulin as in our study.

Insulin resistance may be considered a cardiovascular risk marker for several reasons. First, it is associated with and predicts the incidence of impaired glucose tolerance or diabetes, hypertension, decreased HDL cholesterol and/or increased triglyceride concentration, central obesity, and hyperuricemia.[35] Second, a cluster of these abnormalities is frequently observed in the same individual, ie, the so-called metabolic syndrome.[36] Third, hyperinsulinemia (as an index of insulin resistance) is an independent predictor of morbidity and mortality for coronary heart disease.[2,37] Since in the present study most of the components of the metabolic syndrome were used as exclusion criteria, it is remarkable that the association of insulin resistance with early myocardial infarction remains evident. This finding indicates that insulin resistance may be considered as a candidate risk factor for juvenile myocardial infarction.

Indeed, the association between insulin resistance and early myocardial infarction does not imply a cause-effect relationship. Our patients showed other cardiovascular risk factors including smoking, higher levels of apoB and lower levels of HDL cholesterol and apoA1 (Table 1), which are implicated in the pathogenesis of myocardial infarction.[12,15,16,27] Furthermore, a reduction of cardiovascular events following an effective treatment of insulin resistance has never been proved. Until these points are clarified, the possibility that insulin resistance is merely a risk marker instead of a risk factor for early myocardial infarction cannot be excluded.

The relation between insulin resistance and lipid abnormalities (reduced HDL cholesterol and apoA1 and increased apoB) deserves comment. A reduced suppression of lipolysis by insulin leads to excessive free fatty acid release, which in turn impairs insulin-mediated glucose disposal; a reduced activation of lipoprotein lipase by insulin leads to decreased transfer of cholesterol into HDL and increased removal of cholesteryl ester from HDL, with the final consequence of low HDL cholesterol; a reduced suppression of hepatic very–low-density lipoprotein secretion by insulin is associated with decreased intrahepatic apoB degradation, leading to increased apoB levels; and increased apoA1 levels may result from reduced hepatic synthesis of apoA1 or increased apoA1 degradation. Whether lipid abnormalities are secondary to insulin resistance or vice versa is still unclear.[38]

We found no significant correlation between S_I and the severity of coronary artery disease. This finding is not surprising in view of the high prevalence of coronary arteries that were angiographically normal (28%) or affected by single-vessel disease (44%) in the present study (Table 2) and others.[10-13]

As for hyperinsulinemia, fasting serum insulin and C-peptide values were slightly but not significantly higher in patients than in the control subjects. However, hyperinsulinemia became evident during the FSIGT: the insulin AUC was higher in patients versus controls, confirming previous results obtained by different methods in subjects with early myocardial infarction.[26,27] Hyperinsulinemia may result from increased β-cell secretion and/or decreased hepatic insulin degradation. Another new finding from this study is the quantification of β-cell secretion, hepatic insulin extraction, and peripheral clearance

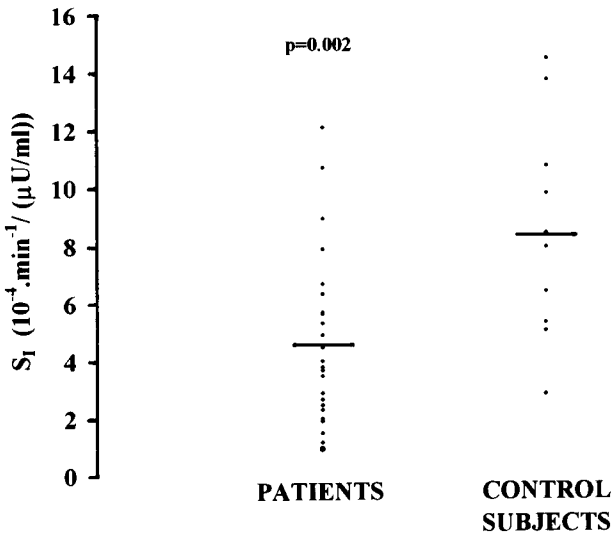

Fig 2. Individual values for S_I in 25 patients with early myocardial infarction and 10 control subjects. Horizontal bars indicate the mean value. Results were analyzed by Student's *t* test.

of C-peptide (k_{o1}) to clarify the mechanism responsible for hyperinsulinemia. Increased β-cell secretion can be demonstrated via a model-independent measure, ie, the C-peptide AUC, which was significantly higher in patients than in control subjects. The model-derived analysis of insulin and C-peptide kinetics provides direct and quantitative measurements of the components of pancreatic secretion. The total amount of insulin release by the β cell over 240 minutes (TIS) was 2-fold greater in patients than in controls. Since the sensitivities of the first and second phase of dynamic (suprabasal) β-cell secretion (Φ_1 and Φ_2) were not changed, the increase of insulin secretion in our patients is mainly due to the basal component, as shown by the increase in the BSR. This can be seen only by exploiting a dynamic test that allows the segregation of the various components of the β-cell secretory pattern and an estimation of the fractional clearance of C-peptide (k_{01}). Normal and similar values of C-peptide clearance confirm that the main reason for elevated C-peptide levels is an increase of β-cell release. C-peptide levels were slightly but not significantly higher in the patients, whereas the basal C-peptide secretion rate (BSR) was significantly increased in the patients. These results are surprising since the fractional clearance of C-peptide (k_{01}) was similar in the two groups. This apparent discrepancy may be explained by the calculations used to obtain these parameters. In our model, the BSR is obtained by multiplying the C-peptide basal concentration by k_{o1}. Even though C-peptide and k_{o1} values were not significantly different when considered separately, after the calculations, their product (ie, their synergistic effect) is significantly different in the two groups.

In our patients, the increase of β-cell secretion was associated with higher levels of serum insulin throughout the test (insulin AUC). Since hepatic insulin extraction (Hm) was not decreased, we may conclude that in patients with early myocardial infarction an increase in β-cell secretion, probably due to the slightly higher glucose levels, appears to be the mechanism mainly responsible for hyperinsulinemia. Hyperinsulinemia due to β-cell hypersecretion is generally viewed as a compensatory mechanism for the reduced insulin action, and has been described in several conditions of insulin resistance including coronary heart disease.[39]

Insulin clearance is typically reduced in insulin resistance. We found an increase in insulin secretion (TIS) combined with an increase in hepatic insulin extraction, suggesting an increase of total insulin clearance. This atypical finding has been reported in other conditions of insulin resistance, such as hypertension,[40] steroid treatment,[41] and hyperparathyroidism.[42] A hypothetic mechanism at the hepatic level to compensate for hyperinsulinemia was suggested and may apply also to this study.

In summary, the present study indicates that early myocardial infarction is associated with insulin resistance, and hyperinsulinemia depends mainly on an increase of β-cell secretion. These findings were evident in the absence of other factors known to reduce insulin sensitivity. The FSIGT may be considered a useful test to reveal and quantify insulin resistance even in patients with fasting normoglycemia and normal glucose tolerance.

REFERENCES

1. De Fronzo RA, Ferrannini E: Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. Diabetes Care 14:173-194, 1991
2. Despres JP, Lamarche B, Mauriege P, et al: Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 334:952-957, 1996
3. Ronnemaa T, Laakso M, Pyorala K, et al: High fasting plasma insulin as an indicator of coronary heart disease in non–insulin-dependent diabetic patients and non diabetic subjects. Arterioscler Thromb 11:80-90, 1991
4. Ariza CR, Frati AC, Gomez G, et al: Hyperinsulinemia in patients with coronary heart disease in absence of overt risk factors. Arch Med Res 28:115-119, 1997
5. Seibaek M, Sloth C, Vallebo L, et al: Glucose tolerance status and severity of coronary artery disease in men referred to coronary arteriography. Am Heart J 133:622-629, 1997
6. Spallarossa P, Cordera R, Andraghetti G, et al: Association between plasma insulin and angiographically documented significant coronary artery disease. Am J Cardiol 74:177-179, 1993
7. Laakso M, Sarlund H, Salonen R, et al: Asymptomatic atherosclerosis and insulin resistance. Arterioscler Thromb 11:1068-1076, 1991
8. Howard G, O'Leary DH, Zaccaro D, et al: Insulin sensitivity and atherosclerosis. Circulation 93:1809-1817, 1996
9. Bressler P, Bailey SR, Matsuda M, et al: Insulin resistance and coronary artery disease. Diabetologia 39:1345-1350, 1996
10. Fournier JA, Sanchez A, Quero J, et al: Myocardial infarction in men aged 40 years or less: A prospective clinical-angiographic study. Clin Cardiol 19:631-636, 1996
11. Sharifi M, Frohlic TG, Silverman IM: Myocardial infarction with angiographically normal coronary arteries. Chest 107:36-40, 1995
12. Zimmerman FH, Cameron A, Fisher LD, et al: Myocardial infarction in young adults: Angiographic characterization, risk factors and prognosis (Coronary Artery Surgery Study Registry). J Am Coll Cardiol 26:654-661, 1995
13. Kanitz MG, Giovannucci SJ, Jones JS, et al: Myocardial infarction in young adults: Risk factors and clinical features. J Emerg Med 14:139-145, 1996
14. Hoit BD, Gilpin EA, Henning H, et al: Myocardial infarction in young patients: An analysis by age subsets. Circulation 74:712-721, 1986
15. Barbash GI, White HD, Modan M, et al: International Tissue Plasminogen Activator/Streptokinase Mortality Trial: Acute myocardial infarction in the young—The role of smoking. Eur Heart J 16:313-316, 1995
16. Wolfe MW, Vacek JL: Myocardial infarction in the young. Chest 9:926-930, 1988
17. The Joint International Society and Federation of Cardiology/World Health Organisation Task Force on Standardisation of Clinical Nomenclature: Nomenclature and criteria for diagnosis of ischemic heart disease. Circulation 59:607-609, 1979
18. Gensini GG: A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 51:606-607, 1983
19. Sallis AS, Haskell JD, Paffenbarger R: Physical activity assessment in the Five-City Project. Am J Epidemiol 121:91-106, 1985
20. World Health Organization Study Group: Diabetes mellitus. World Health Organ Tech Rep Ser 727:1-113, 1985
21. Warnick GR, Albers JJ: A comprehensive evolution of the

heparin manganese precipitation procedure for estimating high density lipoprotein cholesterol. J Lipid Res 29:65-76, 1978

22. Friedewald WT, Levy RI, Frederickson DS: Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 18:499-502, 1972

23. Bergman RN: Towards physiological understanding of glucose tolerance. Minimal model approach. Diabetes 38:1512-1527, 1989

24. Pacini G, Cobelli C: Estimation of β-cell secretion and insulin hepatic extraction by the minimal modelling technique. Comput Methods Programs Biomed 32:241-248, 1990

25. Pacini G, Bergman RN: MINMOD: A computer program to calculate insulin sensitivity and pancreatic responsivity from frequently sampled IVGTT. Comput Methods Programs Biomed 23:113-122, 1986

26. Bavenholm P, Proudler A, Tornvall P, et al: Insulin, intact and split proinsulin, and coronary artery disease in young men. Circulation 92:1422-1429, 1995

27. Bavenholm P, Karpe F, Proudler A, et al: Association of insulin and insulin propeptides with an atherogenic lipoprotein phenotype. Metabolism 44:1481-1488, 1995

28. Carey DG: Abdominal obesity. Curr Opin Lipidol 9:35-40, 1998

29. Facchini FS, Hollenbeck CB, Jeppesen J, et al: Insulin resistance and cigarette smoking. Lancet 339:1128-1130, 1992

30. Eliasson B, Attvall S, Taskinen M-R, et al: The insulin resistance syndrome in smokers is related to smoking habits. Arterioscler Thromb 14:1946-1950, 1994

31. Cobelli C, Pacini G: Insulin secretion and hepatic extraction in humans by a minimal modeling of C-peptide and insulin kinetics. Diabetes 37:223-231, 1988

32. Bergman RN, Prager R, Volund A, et al: Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. J Clin Invest 79:790-800, 1987

33. Polonsky KS, Rubenstein AH: C-peptide as a measure of the secretion and hepatic extraction of insulin: Pitfalls and limitations. Diabetes 33:486-494, 1984

34. Pacini G, Tonolo G, Sambataro M, et al: Insulin sensitivity and glucose effectiveness: Minimal model analysis of regular and insulin-modified FSIGT. Am J Physiol 274:E592-E599, 1998

35. Haffner SM, Valdez RA, Hazuda HP, et al: Prospective analysis of the insulin resistance syndrome (syndrome X). Diabetes 41:715-722, 1992

36. Alberti KGMM, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. I. Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabet Med 15:539-553, 1998

37. Fontbonne A, Charles A, Thibult N, et al: Hyperinsulinemia as predictor of coronary heart disease mortality in a healthy population: The Paris Prospective Study, 15-year follow-up. Diabetologia 34:356-361, 1991

38. Frayn KN: Insulin resistance and lipid metabolism. Curr Opin Lipidol 4:197-204, 1993

39. Reaven GM, Laws A: Insulin resistance, compensatory hyperinsulinemia, and coronary heart disease. Diabetologia 37:948-952, 1994

40. Kautzky-Willer A, Pacini G, Weissel M, et al: Elevated hepatic insulin extraction in essential hypertension. Hypertension 21:646-653, 1993

41. Kautzky-Willer A, Thomaseth K, Clodi M, et al: β-Cell activity and hepatic insulin extraction following dexamethasone administration in healthy subjects. Metabolism 45:486-491, 1996

42. Kautzky-Willer A, Pacini G, Niederle B, et al: Insulin secretion, insulin sensitivity and hepatic insulin extraction in primary hyperparathyroidism before and after surgery. Clin Endocrinol (Oxf) 37:147-155, 1992