

The Relation Between Insulin Resistance Determined by Haemostatic Modelling and Slow Coronary Flow

Zekeriya Nurkalem,^{1MD}, Ahmet L Orhan,^{1MD}, Ahmet T Alper,^{1MD}, Huseyin Aksu,^{1MD}, Murat Ozdamar,^{1MD}, Nevzat Uslu,^{1MD}, Sevkett Gorgulu,^{1MD}, Hakan Hasdemir,^{1MD}, Mehmet Sargin,^{2MD}, Mehmet Eren,^{1MD, FESC}

Abstract

Introduction: In this study, we sought to determine whether insulin resistance, which is investigated by homeostatic modelling, is related to slow coronary flow (SCF). **Materials and Methods:** A total of 24 patients with SCF (4 females/20 males, mean age 47 ± 12 years) and 32 patients with normal coronary artery (10 females/22 males, mean age 52 ± 12 years) were included in the study. Baseline glucose, insulin and plasma lipid levels were measured. A standard oral glucose tolerance test (OGTT) was performed and post-challenge insulin levels were also measured. The index of insulin resistance was calculated with the homeostatic modelling [homeostatic model assessment for insulin resistance index (HOMA-IR)]. **Results:** There were no differences between the 2 groups with regard to age, lipid levels, blood pressure levels, history of smoking, fasting and post-challenge plasma glucose. Baseline insulin levels were augmented in the SCF group (9.64 ± 5.93 vs 7.04 ± 3.26 , $P = 0.041$). HOMA-IR levels were not different between the study groups (2.20 ± 1.44 vs 1.69 ± 0.86 , $P = 0.129$). Manifest insulin resistance was significantly higher in the SCF group as compared with the control group (25% vs 3%, $P = 0.01$). **Conclusion:** Manifest insulin resistance is seen more frequently in patients with SCF.

Ann Acad Med Singapore 2008;37:188-91

Key words: Coronary artery disease, Glucose metabolism, Oral glucose tolerance test

Introduction

Slow coronary flow (SCF) is a well recognised clinical entity, characterised by delayed opacification of coronary arteries in the presence of normal coronary angiogram.¹ Many aetiological factors, such as microvascular and endothelial dysfunction, have been implicated.²⁻⁵ Insulin resistance is related to the vasomotor dysfunction of the endothelial cells. On the other hand, insulin resistance plays an important role in promoting coronary artery disease (CAD) and the degree of insulin resistance is well correlated with the severity of CAD.⁶⁻⁹ The homeostatic model assessment insulin resistance (HOMA-IR) index is a simplified computer-based method used to estimate insulin resistance.¹⁰⁻¹² However, the relationship between SCF and insulin resistance has not yet been established.

The aim of this study was to investigate the relationship between SCF and insulin resistance using homeostatic modelling.

Materials and Methods

Study Population

A total of 24 patients with SCF (4 females/20 males mean age 47 ± 12 years) and 32 patients with normal coronary artery (10 females/22 males, mean age 52 ± 12 years) were included in the study. The baseline glucose, insulin levels and lipid profiles were prospectively evaluated. All patients underwent standard oral glucose tolerance test (OGTT) after which their post-challenge insulin levels were measured. The study and control patients were recruited from 5940 consecutive patients who underwent first diagnostic coronary angiography for evaluation of angina in our centre between December 2004 and May 2005. The exclusion criteria were diabetes mellitus, which was diagnosed according to the American Diabetes Association,¹³ patients with fasting plasma glucose over 110 mg/dL, acute heart failure, comorbid illnesses, hepatic dysfunction, serum creatinine >1.4 mg/dL, or receiving hor-

¹ Siyami Ersek Thoracic and Cardiovascular Surgery Center, Cardiology Department Istanbul, Turkey

² Kartal Lutfi Kirdar Education and Research Hospital, Diabetes Department, Istanbul, Turkey

Address for Correspondence: Dr Zekeriya Nurkalem, Karsli Ahmet Cad. Meskenler Giris Sok. A-Blok No: 10/12 Icerenkoy-Istanbul, Turkey.

Emails: zeknurkalem@yahoo.com, nurkalem@gmail.com

mone replacement therapy, antidiabetic agents or steroid therapy. The study was approved by the local ethics committee of our hospital and all patients gave written informed consent.

Anthropometric Measurements

Weight, height and body mass index (BMI) were measured under standardised conditions.

Exercise Testing

The control group underwent an exercise stress test to eliminate microvascular dysfunction according to American College of Cardiology (ACC)/ American Heart Association (AHA) practice guidelines¹⁴ using a Bruce protocol.¹⁵ The test was considered positive for ischaemia when there was more than 1 mm of down-sloping or horizontal ST depression at 60 to 80 ms after the J point. Patients with positive results were excluded from the study.

TIMI Frame Count and Definition of SCF

Coronary arteriography was performed by a femoral approach using the Judkins catheter and iopromide (Ultravist-370, Schering AG, Berlin, Germany) as contrast agent. For the quantitative measurement of coronary blood flow, the time elapsed from the appearance of the contrast agent until it reached the distal end of either left anterior descending artery (LAD), circumflex artery (Cx) or the right coronary artery (RCA) in terms of cine-frame count was considered to be the thrombolysis in myocardial infarction (TIMI) frame count. Distal end was defined as

distal bifurcation for the LAD and the Cx and first branch of posterolateral artery for RCA. The final count was then subtracted from the initial count and the exact TIMI frame count was calculated for the given artery. However, it was divided by 1.7 when the LAD artery was the case for adjusted correction. The cut-off values were defined according to TIMI frame count method by Gibson et al (36 ± 2.6 for LAD, 22.2 ± 4.1 for Cx, and 20.4 ± 3.0 for RCA).¹⁶

Fasting and Post-challenge Blood Samples

Blood samples were collected from the patients after a 12-hour overnight fasting. All routine biochemical tests were carried out on a Roche Diagnostic Modular Systems autoanalyser. A 75-g glucose load was administered orally to the patients according to World Health Organization (WHO) criteria.¹⁷ Venous blood samples were drawn 10 min before and 120 min after glucose load for analysing glucose and insulin levels. Plasma glucose concentrations were determined by an enzymatic glucose oxidase method (Roche product, Ontario, Canada). Levels of insulin were measured by chemiluminometric immunoassay (DPC-Immunit 2000, cat. No. 152).

Insulin Resistance and Homeostatic Modelling

Insulin resistance was determined from fasting plasma glucose and insulin concentrations, using homeostasis model assessment, by the formula [resistance = insulin/($22.5 \cdot e^{-\ln \text{glucose}}$)] as previously described.^{12,18} Insulin resistance was accepted as $>2.24 \pm 1.26$, as previously described for healthy subjects.¹⁹ Manifest insulin resistance was defined as HOMA-IR >3.5 .¹⁹

Table 1. Patients' Demographic Data

Variable	SCF group	Control group	P
Age (y)	47 $\pm$ 12	52 $\pm$ 12	0.078
Sex (Female/Male)	4/20	10/22	0.212
Family history of coronary artery disease [n (%)]	12 (50)	5 (31.3)	0.240
Hypertension [n, (%)]	12 (50)	16 (50)	0.999
Systolic blood pressure (mmHg)	121.04 $\pm$ 23.50	122.50 $\pm$ 29.38	0.869
Diastolic blood pressure (mmHg)	74.69 $\pm$ 15.43	75.96 $\pm$ 13.90	0.793
Smoker [n (%)]	18 (75)	17 (53.1)	0.737
Waist circumference (cm)	98.04 $\pm$ 11.67	94.79 $\pm$ 5.74	0.223
Body mass index (kg/m ²)	27.68 $\pm$ 4.01	26.12 $\pm$ 2.74	0.121
Total cholesterol (mg/dL)	180.08 $\pm$ 42.29	189.59 $\pm$ 32.04	0.373
Triglyceride (mg/dL)	118.33 $\pm$ 90.78	110.11 $\pm$ 44.51	0.690
High-density lipoprotein (mg/dL)	50.75 $\pm$ 12.17	48.97 $\pm$ 15.91	0.654
Low-density lipoprotein (mg/dL)	104.94 $\pm$ 38.29	118.59 $\pm$ 31.07	0.172
Apolipoprotein-A (mg/dL)	146.94 $\pm$ 17.06	155.22 $\pm$ 34.04	0.303
Apolipoprotein-B (mg/dL)	91.08 $\pm$ 23.51	102.52 $\pm$ 19.42	0.106
Mean TIMI frame count	45.20 $\pm$ 21.26	14.54 $\pm$ 7.79	<0.001

SCF: slow coronary flow; TIMI: thrombolysis in myocardial infarction

Table 2. Glucometabolic Parameters and Insulin Resistance Data

Variable	SCF group	Control group	P
Fasting plasma glucose (mg/dL)	91.46 ± 9.83	94.41 ± 14.91	0.378
Fasting insulin (U/L)	9.64 ± 5.93	7.04 ± 3.26	0.041
Post-challenge glucose (mg/dL)	105.13 ± 39.01	112.00 ± 30.72	0.480
Post-challenge insulin (U/L)	39.15 ± 28.97	40.64 ± 32.38	0.903
HOMA-IR	2.20 ± 1.44	1.69 ± 0.86	0.129
The number of patients with insulin resistance [n (%)]	6 (25)	1 (3)	0.01

HOMA-IR: homeostatic model assessment for insulin resistance; SCF: slow coronary flow

Statistical Analysis

Data were expressed as mean ± SD or geometric mean (95% confidence interval). SCF and control groups were analysed using unpaired *t*-tests for parametric data. Categorical data were analysed using χ^2 or Fisher's exact test. The association between insulin resistance and all other parameters were first analysed by univariate analysis. Multivariate analysis to evaluate associations of SCF was performed using multivariate stepwise logistic regression test. All calculations were performed using the Statistical Package for the Social Sciences programme (SPSS 10.00, Chicago, IL). A *P* value <0.05 was considered statistically significant.

Results

Age, sex, history of smoking, BMI, blood pressure, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride and fasting plasma glucose were similar in both groups (Table 1). Although there was no statistical difference between fasting plasma glucose levels and postprandial glucose levels between patients with SCF and controls (91.5 ± 9.8, 105.1 ± 39 mg/dL vs 94.4 ± 14.9, 112 ± 30.7 mg/dL, *P* = 0.378, *P* = 0.48, respectively), fasting insulin levels were significantly higher in patients with SCF as compared to controls (9.64 ± 5.9 vs 7.04 ± 3.26 U/L, *P* = 0.041). The number of patients who had insulin resistance was significantly higher in the SCF patient group [6 (25%) vs 1 (3%), *P* = 0.01]. Study variables of glucometabolic condition and insulin resistance were shown in Table 2. When the cut-off point of HOMA-IR was taken as 2.24, the rate of insulin resistance between the study groups was 31% vs 38% (*P* = 0.4), while it was 3% vs 25% with a cut-off point over 3.5, which indicates overt insulin resistance (*P* = 0.01) (Fig. 1).

In univariate analysis, insulin resistance correlated with triglyceride levels (*r* = 0.42, *P* = 0.002), corrected LAD TIMI frame count (*r* = 0.34, *P* = 0.01) and Cx TIMI frame count (*r* = 0.29, *P* = 0.003). In multivariate analysis, only the corrected LAD frame was related to insulin resistance (odds ratio, 1.054; 95% CI, 1.008 to 1.102; *P* = 0.02).

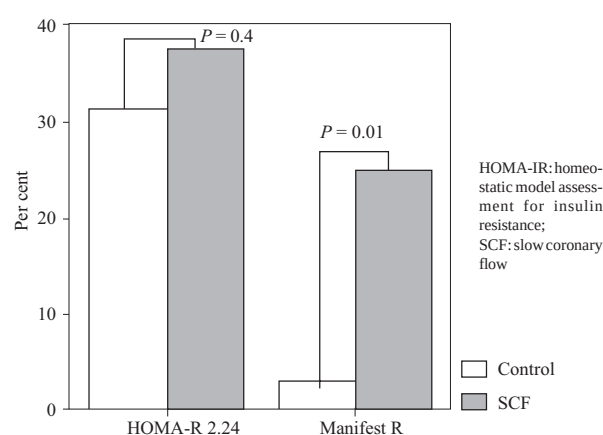


Fig. 1. Distribution of insulin resistance according to HOMA-IR cut-off point in all study groups. Insulin resistance was accepted as >2.24. Manifest insulin resistance was defined as HOMA-IR >3.5.

Discussion

Insulin resistance plays an important role in promoting CAD^{6,7} and the degree of insulin resistance correlates with the severity of CAD.^{8,9} Insulin resistance has been considered to promote arteriosclerosis by directly effecting blood vessels. The relationship between insulin resistance and arteriosclerosis has been studied from various aspects. There are different theories as to how insulin resistance affects CAD.²⁰⁻²²

Insulin resistance is related to the vasomotor dysfunction of the endothelial cells that line the coronary artery.^{23,24} It is well known that endothelial function is impaired in patients with SCF.^{2,25} In our study, we evaluated the effect of impaired glucose metabolism and insulin resistance that may play some role in the pathophysiology of SCF. We found increased fasting insulin levels in patients with SCF and the number of patients with overt insulin resistance to be significantly higher in SCF group (*P* = 0.03). Increased insulin resistance may play at least some role in patients with SCF.

Insulin resistance is involved not only in diabetes mellitus, but also in other pathological states such as obesity and hypertension.^{26,27} In a recently published report, Binak and colleagues²⁸ found a positive correlation between postprandial glycaemia and SCF but they did not mention BMI

and the frequency of obesity in their study population. In our study, where obesity and BMI were not different in the SCF and control group, postprandial glycaemia was not related to SCF. In another study, Yazici et al²⁹ investigated the relationship between the degree of SCF and serum insulin, glucose and lipid levels. As a result, they found no correlations between corrected TIMI frame count and serum insulin, glucose and lipid levels. However, they measured only basal serum insulin, not insulin resistance, without homeostatic models.

On the other hand, evaluating insulin resistance by homeostatic modelling is more reliable than the standard method because both fasting glucose and insulin levels are integrated.¹⁰⁻¹² In our study, we used 3.5 as a reference value for overt insulin resistance as described by Gokcel and his colleagues.¹⁹ The number of patients with overt insulin resistance was higher in the SCF group compared to controls. Furthermore, insulin resistance was found to be an independent predictor of corrected LAD frame count in multivariate analysis. Insulin resistance may play some role in the development of increased microvascular resistance in patients with SCF. Further studies with larger study populations are needed to clarify this issue.

In conclusion, fasting and postprandial glucose levels were not related to SCF in patients without diabetes mellitus. Fasting insulin levels and overt insulin resistance were increased in patients with SCF.

Study Limitations: *The overall sample size of this study is small. Especially the effects of smoking and lipid parameters on insulin resistance and SCF should be evaluated in larger samples. Further studies with larger samples are required to validate our findings.*

REFERENCES

1. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries – A new angiographic finding. *Am Heart J* 1972;84:66-71.
2. Sezgin AT, Sigirci M, Barutcu I, Topal E, Sezgin N, Ozdemir R, et al. Vascular endothelial function in patients with slow coronary flow. *Coronary Artery Dis* 2003;14:155-61.
3. Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histologic evidence for small vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. *Circulation* 1986;7:964-72.
4. Mangieri E, Machiarelli G, Ciavolella M, Barilla F, Avella A, Martinotti A, et al. Slow coronary flow: clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. *Cathet Cardiovasc Diagn* 1996;37:375-81.
5. Erbay AR, Turhan H, Senen K, Yetkin O, Yasar AS, Sezgin AT, et al. Documentation of slow coronary flow by the thrombolysis in myocardial infarction frame count in habitual smokers with angiographically normal coronary arteries. *Heart Vessels* 2004;19:271-4.
6. Shinozaki K, Suzuki M, Ikebuchi M, Hara Y, Harano Y. Demonstration of insulin resistance in coronary artery disease documented with angiography. *Diabetes Care* 1996;19:1-7.
7. Bonora E, Targher G, Zenere MB, Saggiani F, Cacciatori V, Tosi F, et al. Relationship between fasting insulin and cardiovascular risk factors is already present in young men: the Verona Young Men Atherosclerosis Risk Factors Study. *Eur J Clin Invest* 1997;27:248-54.
8. Pyörälä M, Miettinen H, Laakso M, Pyörälä K. Plasma insulin and all-cause, cardiovascular, and noncardiovascular mortality: the 22-year follow-up results of the Helsinki Policemen Study. *Diabetes Care* 2000;23:1097-102.
9. Mizuno T, Matsui H, Imamura A, Numaguchi Y, Sakai K, Murohara T, et al. Insulin resistance increases circulating malondialdehyde-modified LDL and impairs endothelial function in healthy young men. *Int J Cardiol* 2004;97:455-61.
10. Yokoyama H, Emoto M, Fujiwara S, Motoyama K, Morioka T, Komatsu M, et al. Quantitative insulin sensitivity check index and the reciprocal index of homeostasis model assessment are useful indexes of insulin resistance in type 2 diabetic patients with wide range of fasting plasma glucose. *J Clin Endocrinol* 2004;89:1481-4.
11. Ugur-Altun B, Altun A, Tatli E, Arkan E, Tugrul A. Relationship between insulin resistance assessed by HOMA-IR and exercise test variables in asymptomatic middle-aged patients with type 2 diabetes. *J Endocrinol Invest* 2004;27:455-61.
12. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modelling. *Diabetes Care* 2004;27:1487-95.
13. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 1997;20:1183-97.
14. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee to Update the 1997 Exercise Testing Guidelines. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol*. 2002;40:1531-40.
15. Bruce RA. Exercise testing methods and interpretation. *Adv Cardiol* 1978;24:6-15.
16. Gibson CM, Cannon CP, Daley WL, Dodge JT, Alexander BJ, Marble SJ, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 1996;93:879-88.
17. World Health Organization. Diabetes Mellitus: Report of a WHO Study Group. Geneva: WHO, 1985. Tech. Rep. Ser, no. 727.
18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta cell function from fasting glucose and insulin concentration in man. *Diabetologia* 1985;28:412-9.
19. Gokcel A, Baltali M, Tarim E, Bagis T, Gumurdulu Y, Karakose H, et al. Detection of insulin resistance in Turkish adults: a hospital-based study. *Diabetes Obes Metab* 2003;5:126-30.
20. Mansfield MW, Heywood DM, Grant PJ. Circulating levels of factor VII, fibrinogen, and von Willebrand factor and features of insulin resistance in first-degree relatives of patients with NIDDM. *Circulation* 1996;94:2171-6.
21. Han SZ, Ouchi Y, Karaki H, Orimo H. Inhibitory effects of insulin on cytosolic Ca^{2+} level and contraction in the aorta: Endothelium-dependent and -independent mechanisms. *Circ Res* 1995;77:673-8.
22. Seibaek M, Sloth C, Vallebo L, Hansen T. Glucose tolerance status and severity of coronary disease in men referred to coronary arteriography. *Am Heart J* 1997;133:622-9.
23. Watanabe I, Kawamura I, Satoh K, Nagao K, Kushiro T, Kanmatsuse K. Effect of insulin resistance on the endothelial vasomotor function of the coronary artery of nondiabetic patients. *Jpn Circ J* 1999;63:589-92.
24. Inoue T, Matsunaga R, Sakai Y, Yaguchi I, Takayanagi K, Morooka S. Insulin resistance affects endothelium-dependent acetylcholine-induced coronary artery response. *Eur Heart J* 2000;21:895-900.
25. Sezgin M, Barutcu I, Sezgin AT, Gullu H, Turkmen M, Esen AM, et al. Plasma nitric oxide level and its role in slow coronary flow phenomenon. *Int Heart J* 2005;46:373-82.
26. Ascaso JF, Romero P, Real JT, Lorente RI, Martinez-Valls J, Carmena R. Abdominal obesity, insulin resistance, and metabolic syndrome in a patient southern European population. *Eur J Intern Med* 2003;14:101-6.
27. Evrengul H, Dursunoglu D, Kaftan A, Kilicaslan F, Tanriverdi H, Kilic M. Relation of insulin resistance and left ventricular function and structure in non-diabetic patients with essential hypertension. *Acta Cardiol* 2005;60:191-8.
28. Binak E, Gunduz H, Sahin M, Kurtoglu N, Dindar I. The relation between impaired glucose tolerance and slow coronary flow. *Int J Cardiol* 2006;111:142-6.
29. Yazici M, Demircan S, Aksakal E, Sahin M, Meric M, Dursun I, et al. Plasma insulin, glucose and lipid levels, and their relations with corrected TIMI frame count in patients with slow coronary flow. *Turkish Anadolu Kardiyol Derg* 2003;3:227-9.