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Influence of Abnormal Glucose Metabolism on Coronary Microvascular Function After a Recent Myocardial Infarction

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OBJECTIVES This study sought to assess the association between abnormal glucose metabolism and abnormal coronary flow reserve (CFR) in patients with a recent acute myocardial infarction (AMI).

BACKGROUND Mortality and morbidity after AMI is high among patients with abnormal glucose metabolism, which may be related to abnormal microcirculation.

METHODS We studied 183 patients with a first AMI. In 161 patients with no history of diabetes mellitus (DM), an oral glucose tolerance test was performed, and patients were categorized according to World Health Organization criteria for whole blood glucose into 3 groups. After coronary angiography and revascularization, a comprehensive transthoracic echocardiogram and noninvasive assessment of CFR was performed in the distal part of left descending artery, as an indicator of microvascular function. Adenosine was administered by intravenous infusion (140 μg/kg/min) to obtain the hyperemic flow profiles. The CFR was defined as the ratio of hyperemic to baseline peak diastolic coronary flow velocities.

RESULTS Median CFR was 1.9 (interquartile range [IQR] 1.4 to 2.4], and 109 (60%) patients had a CFR $\leq$2. The lowest CFR was seen in patients with a history of DM (1.4 [IQR 1.4 to 1.7], n = 22) and in patients with newly diagnosed DM (1.6 [IQR 1.3 to 2], n = 39), whereas CFR did not differ in patients with abnormal glucose tolerance (2.1 [IQR 1.4 to 2.6], n = 58) and in patients with normal glucose tolerance (2.2 [IQR 1.7 to 2.6], n = 62). In a stepwise logistic regression model adjusting for age, sex, site and size of AMI, heart rate, risk factors of the metabolic syndrome, degree of angiographic evidence of coronary artery disease, and medical therapy, newly diagnosed DM (odds ratio: 3.0) and a history of DM (odds ratio: 9.9) remained significant predictors of CFR $<$2, whereas impaired glucose tolerance was not.

CONCLUSIONS CFR is decreased in patients with known or newly diagnosed DM even after adjustment of possible confounders, whereas CFR in patients with impaired glucose tolerance seems less affected. (Coronary Flow Reserve and Glucometabolic State [CFRGS]; NCT00845468) (J Am Coll Cardiol Img 2009;2:1159–66) © 2009 by the American College of Cardiology Foundation

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There is increasing interest in the association between disturbances in glucose metabolism and patients with heart disease. Utilizing an oral glucose tolerance test (OGTT), several studies have consistently demonstrated that in addition to the 20% of patients with known diabetes mellitus (DM), a further 20% have unrecognized DM, and ≈30% have impaired glucose tolerance (IGT), leaving only 30% with normal glucose metabolism (1). Mortality and morbidity after acute myocardial infarction (AMI) are higher among patients with abnormal glucose metabolism independent of other risk factors (2). The increased mortality is mainly related to a higher incidence of congestive heart failure, which cannot be explained by a more advanced ventricular systolic dysfunction or an increased risk of adverse remodeling (3,4). The long-term prognosis of patients with AMI has improved during the last 2 decades. However, patients with overt DM have not achieved the same improvement in outcome (5). This together with the increasing incidence of type 2 DM (6), underlines the importance of a better understanding of the pathophysiological factors contributing to the increased mortality and morbidity in this large group of patients.

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CFR = coronary flow reserve

DM = diabetes mellitus

IGT = impaired glucose tolerance

LAD = left anterior descending artery

NSTEMI = non–ST-segment elevation myocardial infarction

OGTT = oral glucose tolerance test

OR = odds ratio

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

Consequences of abnormal glucose metabolism are mainly macrovascular and microvascular disease causing organ damage. Myocardial microvascular function can be evaluated by quantification of the coronary flow reserve (CFR). CFR reflects the impact on total coronary resistances in terms of epicardial coronary arteries and the vasodilator capacity of the microcirculation. A noninvasive and reproducible estimate of CFR may be obtained using transthoracic Doppler echocardiography, which has an excellent correlation with CFR measured by position emission tomography and magnetic resonance (7,8) as well as invasive assessment of CFR (9,10). It is, however, uncertain how various degrees of dysglycemia affect CFR in patients with a recent AMI.

Testing the hypothesis that abnormal glucose metabolism is a determinant of depressed CFR in patients with a recent AMI, we studied the relation between glucose metabolism and coronary microvascular function, measured by CFR, in the early phase of first AMI.

METHODS

Study population. Between January 2006 and August 2008, 190 patients with first AMI admitted to the coronary care unit at Funen Hospital, Svendborg, Denmark, were consecutively screened. Inclusion criteria were as follows: 1) documented AMI (dynamic rise in troponin-T >0.1 μg/l, as well as either typical symptoms, characteristic electrocardiographic changes, or both) regardless of location of infarction; 2) a patent left anterior descending artery (LAD) without any stenosis exceeding 50% on angiography; 3) an echocardiographic window allowing the assessment CFR; 4) no contraindications for coronary angiography; and 5) no history of documented prior AMI, coronary bypass surgery, valvular heart disease, or poorly controlled obstructive airway disease. Patients were eligible whether presenting with ST-segment elevation myocardial infarction (STEMI) or with non–ST-segment elevation myocardial infarction (NSTEMI). In addition, patients with anterior AMI were enrolled if the LAD was patent. Three patients were excluded because of significant stenosis in the LAD. Four patients were excluded because of inability to perform CFR. The final study population consisted of 183 patients.

Patients presenting with STEMI within 12 h of onset of symptoms were transferred to a tertiary invasive center where acute percutaneous coronary intervention (PCI) was performed. According to national standard clinical practice, patients were treated with primary PCI, and for no patient was thrombolysis used. For patients presenting with NSTEMI, initial antithrombotic therapy was instituted and subsequent angiography performed within the first week (median 4 days [3 to 6 days]).The study protocol was approved by the Regional Ethics Committee of Southern Denmark and the Danish Data Protection Agency, and written informed consent was obtained from all patients.

Assessment of glucometabolic control. Patients with no history of diabetes had an OGTT performed before discharge, in agreement with the European Society of Cardiology and European Association for the Study of Diabetes. After an overnight fast, a 75-g glucose solution was administered, and capillary whole blood glucose levels were measured using a HemoCue 201+ glucose analyzer (HemoCue AB, Ängelholm, Sweden). Patients were classified according to the 1999 World Health Organization (WHO) criteria for

whole blood glucose levels as having newly detected DM if fasting whole blood glucose was ≥6.1 mmol/l (110 mg/dl) or if the 2-h post-load blood glucose was ≥11.1 mmol/l (200 mg/dl). IGT was defined as a 2-h post-load blood glucose ≥7.8 mmol/l (140 mg/dl) unless fasting whole blood glucose met the criteria for newly detected DM (11,12).

Echocardiography. Transthoracic echocardiography was performed at a median 5 days [IQR 2 to 9 days] after AMI using a commercially available ultrasound system (Vivid 7, GE Medical Systems, Inc., Horten, Norway). All images were analyzed offline by a single investigator, blinded to all clinical data. From standard chamber projections, left ventricular ejection fraction, wall motion score index, left atrial volume index, early transmitral flow velocity to early diastolic mitral annular velocity ratio (E/e′ ratio), early transmitral flow velocity to atrial transmitral flow velocity ratio (E/A ratio), and E-wave deceleration time were obtained (Table 1) (13).

Assessment of CFR. The CFR studies were performed in an angiographically nonobstructed (<50%) LAD. If a significant LAD stenosis was revealed during angiography, CFR was assessed after PCI had been performed. If an obstructed (≥50%) LAD was left untreated, the patient was excluded from the study. Images were obtained in the distal part of the LAD using a 7-MHz transducer. The coronary blood flow was obtained by color Doppler flow-mapping guidance, and a sample volume was positioned within the color signal in the LAD artery by the pulse wave Doppler. After baseline recordings of flow velocity, adenosine was administered by intravenous infusion (140 μg/kg/min) for 90 s, obtaining hyperemic Doppler flow profiles. The CFR was estimated to be the ratio of hyperemic to baseline peak diastolic coronary flow velocities. A CFR >2 was considered normal (14), and the population was dichotomized according to this. All subjects abstained from caffeine-containing drinks for at least 12 h before testing.

All CFR measurements were stored digitally for future offline analysis blinded for all clinical variables. The intraobserver and interobserver variability of coronary flow velocity measurements was 3.6% and 5.3%, respectively.

Laboratory analyses. After an overnight fast, 4 days (range 3 to 8 days) after admission, patients were studied by measuring lipid profile and glucose. Creatine kinase-myocardial band and troponin-T levels were measured at the time of admission and 6 and 12 h after admission.

Statistical analysis. Analyses and sample size calculations were conducted with STATA/MP 10.0 (Stata Corp. LP, College Station, Texas). Data are presented as median (interquartile range [IQR]) and compared using Kruskal-Wallis equality-of-populations rank tests for continuous variables; categorical variables are presented as counts (percentage) and compared using chi-square tests. Because significance tests for baseline characteristics are presented for descriptive purposes only, no adjustment for multiple testing was done.

Univariable logistic regression analysis was used to evaluate the relation between various clinical, echocardiographic, and angiographic variables and CFR. Variables identified in univariable analysis as predictors of an abnormal CFR were subsequently tested in a multivariable model. Data are presented as odds ratios with corresponding 95% confidence intervals. A value of $p < 0.05$ was considered statistically significant.

Sample size calculation was based on available publications that estimated SD for CFR to be 0.5 in both patients with known DM and in healthy controls. To detect a 20% difference between patients with DM (known or newly diagnosed), IGT, and normal glucose metabolism, respectively, with a power of 80% and a 2-sided alpha of 0.05, a total sample size of at least 150 patients was required for the study. We identified 109 patients with abnormal CFR, allowing ≈11 variables to be included in the multivariable model.

RESULTS

Clinical characteristics. We studied 183 patients (median age 63 years [IQR 54 to 70 years]; 132 male, 51 female). OGTT was performed a median of 6 days (IQR 3 to 8 days) after hospital admission. OGTT suggested normal glucose metabolism in 64 (35%) patients and abnormal glucose tolerance in 58 (32%) patients; in 39 (21%) patients, overt DM was diagnosed, and the remaining 22 (12%) patients had a history of DM. Twenty-one of the 39 patients with newly diagnosed DM only had post-prandial hyperglycemia and no fasting capillary blood glucose capillary value >6.1 mmol/l.

Table 1 shows clinical characteristics and medical treatment of the patients according to the glucometabolic groups. Patients with newly detected and known DM were older and included more males. Statins were used more frequently for diabetic patients at hospitalization, likely explaining the lower total cholesterol in this group. The DM group had significantly higher levels of glycosylated hemoglobin (HbA1c).

We found no differences among the 4 groups with respect to Killip classification at admission (p for trend = 0.73), or with respect to type

Table 1. Baseline Characteristics According to Glucometabolic Groups

	Normal Glucose	IGT	New DM	Known DM	p Value*
Patients	64 (35)	58 (32)	39 (21)	22 (12)	
Age, yrs	59.5 [51.5 to 68]	60.5 [53 to 71]	67 [60 to 73]	63 [57 to 75]	0.005
Sex, female/male	15/49	12/46	19/20	5/17	0.01
BMI, kg/m^2	26 [22.6 to 29.1]	27.3 [24.7 to 30.3]	26.8 [23.7 to 29.9]	28.6 [23.2 to 33.3]	0.1
Waist measurement, cm	100 [89 to 109]	102 [94 to 107]	102 [93 to 111]	106.3 [95 to 122.5]	0.09
Systolic BP, mm Hg	130 [120 to 150]	137 [123 to 150]	150 [130 to 164]	140 [115 to 156]	0.2
Diastolic BP, mm Hg	80 [70 to 90]	80 [70 to 90]	80 [70 to 92]	70 [74 to 90]	0.9
Heart rate, beats/min	65 [60 to 75]	65 [60 to 78]	68 [61 to 84]	74 [60 to 100]	0.06
Biochemistry					
Total cholesterol, mmol/l	4.6 [4.1 to 5.5]	4.6 [3.9 to 5.2]	4.3 [3.7 to 5]	3.8 [3.3 to 4.1]	0.004
LDL cholesterol, mmol/l	2.7 [2.3 to 3.4]	2.7 [2.2 to 3.2]	2.6 [1.9 to 3.1]	2.1 [1.8 to 2.4]	0.003
HDL cholesterol, mmol/l	1.1 [0.9 to 1.4]	1.0 [0.9 to 1.5]	1.0 [0.9 to 1.2]	1.1 [0.8 to 1.3]	0.4
Triglycerides, mmol/l	1.30 [0.86 to 1.63]	1.26 [0.86 to 1.71]	1.35 [1.05 to 1.75]	1.31 [1.14 to 1.57]	0.9
fBG plasma, mmol/l	5.4 [5.1 to 5.7]	5.5 [5.2 to 5.9]	6.4 [5.8 to 6.8]	7.7 [5.5 to 9.7]	0.0001
HbA1c, %	5.6 [5.4 to 5.7]	5.6 [5.3 to 5.8]	5.9 [5.6 to 6.3]	7.0 [6.5 to 7.9]	0.0001
Metabolic syndrome†					
Metabolic syndrome	22 (34)	30 (51)	28 (71)	15 (68)	0.005
Waist measurement above definition	44 (69)	48 (83)	35 (90)	19 (86)	
Triglycerides >1.7 mmol/l	11 (17)	15 (26)	10 (26)	4 (18)	
HDL cholesterol below definition	32 (50)	30 (52)	25 (64)	13 (59)	
Systolic BP ≥130 mm Hg	23 (36)	27 (47)	24 (62)	9 (41)	
Diastolic BP ≥85 mm Hg	10 (16)	11 (19)	9 (23)	4 (18)	
fBG plasma, mmol/l	17 (27)	24 (41)	32 (82)	16 (73)	
Prior diagnosis of DM	0 (0)	0 (0)	0 (0)	22 (100)	
Median of metabolic syndrome factors, n	2 [1 to 3]	3 [2 to 4]	4 [3 to 5]	5 [5 to 6]	
Treatment at admission					
Acetylsalicylic acid	5 (7.8)	6 (10.3)	6 (15.4)	7 (31.8)	0.01
Beta-blockers	7 (10.9)	6 (10.3)	7 (17.9)	4 (18.2)	0.15
Clopidogrel	0 (0)	0 (0)	0 (0)	1 (4.5)	0.02
Statins	9 (14.1)	6 (10.3)	3 (7.7)	9 (40.9)	0.001
ACE inhibitors	7 (10.9)	8 (13.8)	4 (10.3)	6 (27.3)	0.064
Ca^{2+}-blockers	7 (10.9)	1 (1.7)	6 (15.4)	4 (18.2)	0.02
Diuretics	9 (14.1)	6 (10.3)	9 (23.1)	9 (40.9)	0.004
Oral antidiabetic agents	0 (0)	0 (0)	0 (0)	12 (54.5)	<0.0001
Insulin therapy	0 (0)	0 (0)	0 (0)	7 (31.8)	<0.0001
Echocardiography					
LVEF, %	54 [43 to 59]	54.6 [42 to 60]	51 [43 to 58]	49.9 [42 to 57]	0.8
WMSI	1.13 [1 to 1.41]	1.06 [1 to 1.44]	1.25 [1 to 1.63]	1.41 [1.14 to 1.56]	0.13
LA index volume, ml/m^2	33.7 [26.5 to 39.6]	33.7 [28.2 to 40.6]	32.6 [24.4 to 36.8]	35.7 [29.1 to 44.4]	0.31
E/e′	9.3 [7.9 to 11.2]	10.3 [8.7 to 12.3]	11.4 [10.5 to 13.8]	10.9 [8.2 to 17.1]	0.0013
E/A ratio	1.01 [0.84 to 1.4]	1.07 [0.89 to 1.31]	0.95 [0.75 to 1.08]	1.125 [0.75 to 1.29]	0.14
E-wave deceleration time, ms	181 [157 to 202]	168 [143 to 197]	185 [167 to 227]	198 [147 to 247]	0.14
Coronary flow reserve	2.04 [1.72 to 2.55]	2.02 [1.44 to 2.65]	1.63 [1.3 to 2]	1.42 [1.13 to 1.67]	0.0001

Values are n (%) or median [interquartile range]. *The p values in this table expressed the trend across groups. †Metabolic syndrome is defined according to the International Diabetes Federation.
ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; DM = diabetes mellitus; E/A ratio = early transmitral flow velocity to atrial transmitral flow velocity ratio; E/e′ = early transmitral flow velocity to early diastolic mitral annular velocity ratio; fBG = fasting blood glucose; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; IGT = impaired glucose tolerance; LA = left atrium; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; WMSI = wall motion score index.

(STEMI vs. NSTEMI), enzymatic size, and location of infarction (p values for trend = 0.16, 0.46, and 0.37, respectively).

For STEMI patients, echocardiography was performed 5 days (IQR 3 to 6 days) after admission, compared with 7 days (IQR 2 to 11 days) for patients with NSTEMI (p = 0.02) (Table 2). The time interval between the onset of symptoms and the performance of echocardiography, including measurement of CFR, did not differ among the study groups. We

found no differences in echocardiographic parameters between the glucometabolic groups concerning left ventricular ejection fraction, wall motion score index, left atrial volume, E/A ratio, and mitral wave deceleration time (p values for trend = 0.8, 0.13, 0.31, 0.14, and 0.14, respectively). We found a trend toward an increased E/e′ according to worsening glucometabolic state (p for trend = 0.0013) (Table 1).

Coronary flow reserve. Median CFR was 1.9 (IQR 1.4 to 2.4). In 109 (60%) patients, a CFR ≤2 was found. The lowest CFR, 1.4 (IQR 1.4 to 1.7), was detected in patients with a known history of DM. CFR was also reduced in patients with newly diagnosed DM (1.6 [IQR 1.3 to 2], p = 0.09) versus a known history of DM, but no difference was observed in patients with abnormal glucose tolerance (2.1 [IQR 1.4 to 2.6]) and normal glucose tolerance (2.2 (IQR 1.7 to 2.6]) (Fig. 1).

Patients with a decreased CFR (<2) were older and had a significantly lower heart rate and higher diastolic blood pressure than did patients with normal CFR (Table 3). In patients revascularized in the LAD, CFR was 1.9 (IQR 1.3 to 2.3) compared with patients not revascularized in the LAD (1.9 [IQR 1.5 to 2.6], p = 0.11). There was no difference in CFR between STEMI patients (1.91 [IQR 1.5 to 2.4]) and NSTEMI patients (1.96 [IQR 1.4 to 2.4], p = 0.38) (Table 2).

Performing a chi-square analysis across all subsets of glucometabolic groups, we found a significant increase in patients with CFR <2 (p < 0.0001).

Furthermore, in a stepwise logistic regression model adjusting for age, sex, site of AMI, size of AMI (peak creatine kinase-myocardial band), heart rate, risk factors for the metabolic syndrome, degree of angiographic evidence of coronary artery disease, and relevant medical therapy, newly diagnosed DM (odds ratio: 3.0 [95% confidence interval: 1.1 to 8.7], p = 0.049) and a known history of DM (odds ratio: 9.9 [95% confidence interval: 1.5 to 73.3], p = 0.03) remained significant predictors of CFR <2, whereas impaired glucose tolerance was not (Fig. 2).

Angiographic and angioplasty data. Angiographic data are presented in Table 4. In 127 patients, successful PCI was performed. Thirty-three patients did not undergo PCI, and among those, 10 underwent subsequent coronary artery bypass surgery. In 23 patients, angiography did not reveal significant stenoses (<50%). In 74 patients, PCI was performed in the LAD; 69 patients achieved Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in the LAD, and 5 achieved TIMI flow grade 0 to 2. Drug-eluting stents were implanted in 140 patients, and 63 patients received eptifibatid/abciximab infusion during and after the PCI procedure. No differences in the number of diseased vessels and TIMI flow grade before and after intervention were seen in patient groups (Table 4).

Table 2. Baseline Characteristics According to STEMI Versus NSTEMI

	STEMI	NSTEMI	p Value
Patients	94 (51)	89 (49)	0.8
Sex, female/male	20/74	31/58	0.11
CFR	1.91 [1.5 to 2.4]	1.96 [1.4 to 2.4]	0.38
WMSI	1.19 [1 to 1.63]	1.14 [1 to 1.44]	0.3
LVEF, %	53.5 [41 to 60]	53.8 [44 to 58]	0.2
Time from admission to revascularization, h	1.5 [0.5 to 2.5]	102 [75 to 137.5]	0.0001
Time from admission to estimation of CFR, days	5 [3 to 6]	7 [2 to 11]	0.02
Culprit lesion			
Left anterior descending artery	45 (48)	40 (45)	0.7
Right coronary artery	35 (37)	30 (34)	0.7
Left circumflex artery	14 (15)	19 (21)	0.3

Values are n (%) or median [interquartile range].
CFR = coronary flow reserve; NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Table 1.

DISCUSSION

Although substantial evidence supports the premise that hyperglycemia affects the coronary microcirculation, this is the first study to assess the impact of known DM, newly diagnosed DM, and IGT on CFR in a consecutive population with a recent AMI. We demonstrate that noninvasive assessment

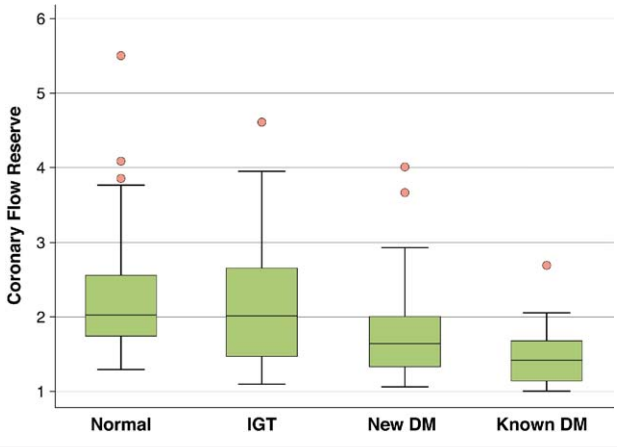

Figure 1. CFR According to Glucometabolic Status

Box plot of the mean values of coronary flow reserve (CFR) according to glucometabolic status. The mean value of CFR is gradually decreased according to worsening glucometabolic state and illustrates the degree of disturbed microvascular function in dysglycemic patients. DM = diabetes mellitus; IGT = impaired glucose tolerance.

Table 3. Baseline Characteristics According to CFR

	CFR ≤2	CFR >2	p Value
Patients	109 (59.6)	74 (40.4)	
Age, yrs	64 [57 to 73]	58 [51 to 68]	0.003
Sex, female/male	34/75	17/57	0.2
Systolic BP, mm Hg	140 [120 to 160]	135 [120 to 150]	0.75
Diastolic BP, mm Hg	80 [70 to 90]	80 [72 to 90]	0.59
Heart rate, beats/min	66 [60 to 75]	61 [54 to 68]	0.002
Current smoker	55 (50.5)	43 (58.1)	0.3
Killip class ≥II	22 (20.2)	6 (8.1)	0.8
Biochemistry			
fBG plasma, mmol/l	5.7 [5.3 to 6.5]	5.6 [5.2 to 6.1]	0.3
HbA1c, %	5.8 [5.5 to 6.3]	5.6 [5.4 to 5.9]	0.01
Peak creatine kinase-MB, μg/l	59.1 [20.8 to 174.5]	49.1 [19.6 to 144]	0.3
Troponin-T	1.02 [0.41 to 4.95]	0.94 [0.33 to 2.47]	0.1
Oral glucose tolerance test, mmol/l			
fBG capillary	5.2 [4.6 to 5.7]	5.1 [4.6 to 5.6]	0.6
2-h capillary glucose	9.2 ± 3.0	7.9 [6.6 to 8.8]	0.0007
Echocardiography			
LVEF, %	52 [41 to 56]	56 [45 to 60]	0.02

Values are n (%) or median [interquartile range].
MB = myocardial band; other abbreviations as in Tables 1 and 2.

of CFR is feasible for a large consecutive population with AMI. In addition, the study demonstrates a persistent association between depressed CFR and overt or newly diagnosed DM after adjustment of possible confounders. However, we were unable to demonstrate a similar association in patients with IGT in whom CFR was no different from CFR in patients with normal glucose metabolism.

Hyperglycemia has been shown to suppress coronary microcirculation in healthy young adults (15). Several mechanisms may explain the association between hyperglycemia and microvascular dysfunction. Persistent hyperglycemia may cause microvascular dysfunction through leukocyte capillary plugging, enhanced platelet activation, and accumulation of advanced glycation products (16,17).

A puzzling finding was that CFR was not depressed in patients with IGT compared with patients with normal glucose metabolism. Other groups have observed abnormal microvascular function in patients with IGT (18), although the diagnosis was made on the basis of admission glucose levels rather than on an OGTT. In our study, the lack of association may be a result of heterogeneity. These patients may represent a mixture of persons with larger infarcts, with resulting stress hyperglycemia, as well as patients with pre-existing IGT (19). We found no difference in HbA1c, and this could confirm that longstanding hyperglycemia was not present in the majority of patients with IGT. HbA1c may be normal despite post-prandial hy-

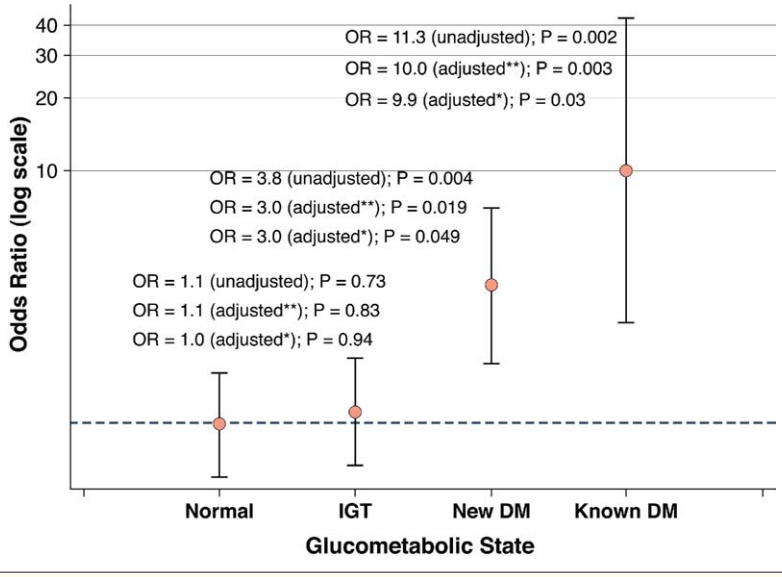

Figure 2. Odds Ratios for CFR <2 According to Glucometabolic Status

Unadjusted and adjusted (not illustrated) odds ratios (OR) for coronary flow reserve (CFR) <2 according to metabolic groups. The figure illustrates the exponential increase for CFR <2 in OR according to glucometabolic state. *The adjusted OR is not illustrated. The OR is adjusted for age, sex, location of infarction, type of infarction, infarct size (peak creatine kinase-myocardial band [mikrg/l]), heart rate, metabolic syndrome risk factors, degree of angiographic coronary artery disease, and relevant drug therapy. **The age- and sex-adjusted OR is not illustrated. Abbreviations as in Figure 1.

perglycemia, which may play a significant role in the development of both microvascular and macrovascular complications (20).

In hearts with acute infarct, basal and hyperemic blood flow may be reduced not only in the infracted area but also in remote segments of the myocardium. We also found reduced CFR in the LAD territory in many patients whose LAD was not the culprit, and that may be representative of decreased microvascular function in the entire heart. The underlying mechanisms may include compromised microcirculation due to myocardial stunning in the infarct zone and intramyocardial edema causing partial obliteration of the microvasculature and a disturbed perfusion of the non-necrotic tissue (21).

In the present study, OGTT suggested normal glucose tolerance in only one-third of the patients. This finding corresponds well with other observational studies (22). Our results indicating microvascular disease in patients with DM is in agreement with previous studies of DM patients without overt ischemic heart disease (23) in which CFR was demonstrated to be impaired even in the absence of significant epicardial coronary atherosclerosis (24).

To further characterize and to assess whether the microvascular abnormalities in dysglycemic patients with a recent MI represent reversible or irreversible changes in the microvascular function, future studies should include serial measurements to assess temporal changes in microcirculation and furthermore assess myocardial viability.

Study limitations. Timing of echocardiography was different in patients with STEMI and NSTEMI. The measurements of CFR were performed with a delay in the NSTEMI group who underwent angiography after initial stabilization, compared with the STEMI group who underwent urgent PCI. Furthermore, the rather large time span was caused by the local logistical arrangement, as described in the Methods section. Although we found no clear association between the timing of CFR and the timing of revascularization, we cannot exclude a bias due to timing of the investigations.

We observed a larger number of patients with 2-vessel disease in the group with diminished microvascular circulation, although not present at the time of CFR measurement. Our finding may reflect increased microvascular dysfunction with increased macrovascular disease. Furthermore, we note the relative low median CFR that may be a result of the confounding mechanism caused by microvessel impairment in post-AMI patients.

Table 4. Angiographic Characteristics

	CFR ≤2 (n = 109)	CFR >2 (n = 74)	p Value
No significant vessel disease, n (%)	7 (6.4)	8 (10.8)	0.06
1 vessel disease, n (%)	65 (59.6)	48 (64.9)	0.5
2 vessel disease, n (%)	28 (25.7)	14 (18.9)	0.3
3 vessel disease, n (%)	9 (8.3)	4 (5.4)	0.5
Left main stem included, n (%)	7 (6.4)	3 (4.1)	0.2
Culprit lesion, n (%)			
Left anterior descending	45 (41.3)	29 (39.2)	0.8
Right coronary artery	46 (42.2)	37 (36.5)	0.5
Left circumflex	18 (16.5)	18 (24.3)	0.1
Coronary angiography before intervention			
TIMI flow grade, n (%)			
0	44 (40.4)	30 (40.5)	0.9
1/2	4/17 (3.6/15.6)	5/9 (6.7/12.3)	0.3/0.5
3	44 (40.4)	30 (40.5)	0.9
Coronary angiography after intervention			
TIMI flow grade, n (%)			
0	3 (2.75)	0 (0)	0.2
1/2	0/3 (0/2.75)	2/3 (2.7/4.1)	0.08/0.6
3	103 (94.5)	69 (92.2)	0.5

CFR = coronary flow reserve; TIMI = Thrombolysis In Myocardial Infarction.

Although assessment of CFR has been validated against invasive measures of CFR, the accuracy is influenced by the image quality and angle dependence of Doppler velocities that may limit the exactness in the individual patient.

Finally, it is mandatory to take the heart rate into account during measurement of CFR. An increased heart rate demands more oxygen to the myocardium. By autoregulatory mechanisms, the recruitment of the microvasculature increases, resulting in decreased CFR (25).

Clinical implications. The present study suggests that CFR is reduced in patients with known or newly diagnosed DM, even after adjustment for possible confounders. Given the difficulties in risk-stratifying diabetic patients, considering that conventional stress testing by wall-motion analyses inadequately identifies high-risk patients (26,27), CFR may prove to be a valuable tool to assess risk for this subset of patients.

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Key Words: coronary flow reserve ■ transthoracic echocardiography ■ acute myocardial infarction ■ dysglycemia ■ impaired glucose tolerance ■ oral glucose tolerance test.