Increased Heat Generation From Atherosclerotic Plaques in Patients With Type 2 Diabetes

An increased local inflammatory activation

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OBJECTIVE — Patients with coronary artery disease (CAD) and diabetes show increased inflammatory activation. Thermography detects local inflammatory involvement as heat generation. The aim of this study was to investigate whether patients with CAD and diabetes have increased local heat generation compared with nondiabetic patients.

RESEARCH DESIGN AND METHODS — We enrolled patients undergoing percutaneous coronary interventions: 45 diabetic patients and 63 nondiabetic patients, serving as the control group, matched for age, type of clinical syndrome, statin and aspirin intake, and angiographic stenosis (%). Coronary thermography was performed, and temperature difference (ΔT) between the atherosclerotic plaque and the proximal vessel wall was measured.

RESULTS — Patients with diabetes had increased temperature difference compared with nondiabetic patients (ΔT: 0.17 ± 0.18°C vs. 0.09 ± 0.02°C, $P = 0.01$). Twenty-one diabetic and 22 nondiabetic patients suffered from acute coronary syndromes (ACSs) ($P = 0.22$). Patients with diabetes and ACSs had increased temperature difference compared with nondiabetic patients with ACSs (ΔT: 0.29 ± 0.31°C vs. 0.15 ± 0.21°C, $P = 0.02$), which is the same as patients with diabetes and chronic stable angina (ΔT: 0.09 ± 0.08°C vs. 0.05 ± 0.04°C, $P = 0.006$). Twenty-three diabetic and 30 nondiabetic patients were under therapy with statins ($P = 0.72$). Patients with diabetes under statins had lower temperature difference compared with untreated patients (ΔT: 0.11 ± 0.12°C vs. 0.22 ± 0.21°C, $P = 0.02$), which is the same as nondiabetic patients under statins (ΔT: 0.05 ± 0.04°C vs. 0.13 ± 0.18°C, $P = 0.01$).

CONCLUSIONS — Patients with diabetes have increased temperature difference compared with nondiabetic patients. Patients with diabetes under statins showed decreased temperature difference compared with untreated patients, suggesting that statins have a favorable effect in patients with diabetes and CAD.

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I nflammation, known to play a key role in coronary artery disease (CAD) progression, is significantly pronounced in the presence of diabetes. Higher levels of inflammatory indexes and adhesion molecules are detected in patients with diabetes and CAD compared with nondiabetic patients with CAD and healthy control subjects. More recent data (1,2) implicate these higher levels in the prognosis in cardiovascular disease.

Coronary thermography is a method for detection of inflammatory status locally. Several ex vivo and in vivo studies showed a correlation between inflammatory involvement and heat production in atherosclerotic plaques of animal and human subjects (3–7). Recent studies (6,8) revealed a positive correlation between the concentration of macrophages within atheroma and plaque temperature. Moreover, the anti-inflammatory effect of either dietary cholesterol lowering or administration of statins was shown to be associated with reduction of local plaque thermal heterogeneity in animals and humans, respectively (6,9).

The impact of type 2 diabetes, however, on coronary plaque temperature has not been investigated. Thus, the aim of the present study was to investigate *1*) whether culprit coronary plaques in patients with type 2 diabetes have increased thermal heterogeneity compared with patients without diabetes, *2*) the impact of clinical syndrome on plaque thermal heterogeneity of patients with type 2 diabetes, and *3*) whether statins have a favorable effect on atherosclerotic plaque temperature of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — In this study, we prospectively enrolled patients with type 2 diabetes undergoing percutaneous coronary intervention. As a control group, for every patient with type 2 diabetes 1.5 nondiabetic patients were scheduled to be included in the study. Patients were excluded if they suffered from cardiogenic shock; if they had allergy to aspirin, heparin, or clopidogrel; if there was evidence of intercurrent inflammatory or neoplasmatic condition likely to be associated with an acute-phase response; if they were being treated with an immune sup-

pressive agent, corticosteroids, or nonsteroidal anti-inflammatory drugs, except for aspirin; or if treatment with a glycoprotein IIb/IIIa inhibitor was employed within the previous 30 days.

Angiographic inclusion criteria for both groups were one significant de novo angiographic lesion (≥50%) <20 mm in length with reference vessel diameter ≥2.5 mm. The culprit lesion was identified by the association of precrisis and intercrisis electrocardiograms, left ventricle wall motion abnormalities, and angiographic lesion appearance. Two experienced cardiologists (E.T., M.V.) independently reviewed all clinical and angiographic data to decide angina status before the procedure.

Informed consent was obtained from all patients. The institutional ethics committee approved the protocol. The investigators carried out the investigation in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Clinical characteristics

Risk factors included hypertension (medication treated), hypercholesterolemia (treated or ≥200 mg/dl), and current smoking. Diabetes was defined as a fasting blood glucose level >140 mg/dl in ≥2 different values. Patients had known diabetes for 8.2 ± 4.3 years at the time of the intervention and were treated with insulin or an oral hypoglycemic agent for at least 1 month before coronary intervention. There was no change in frequency, duration, or intensity of symptoms of stable angina within the last 6 weeks. Acute coronary syndrome (ACS) included patients with unstable angina or acute myocardial infarction. Unstable angina was defined as angina at rest, new-onset angina, or an increase in the severity of angina in the previous month (with negative cardiac markers). Previous myocardial infarction (<6 weeks), coronary artery bypass grafting, percutaneous coronary intervention in other lesions, and the left ventricular function were tabulated. Statin administration was considered when patients were treated with statins for >4 weeks.

Angiographic analysis

Coronary angiograms were analyzed with a computer-assisted, automated-edge detection algorithm (Medcon, Tel Aviv, Israel), using standard qualitative and quantitative definitions and measurements. The outer diameter of the contrast-

filled catheter was used for calibration, and the minimal lumen diameter was obtained from the single "worst" view.

Temperature measurements

Coronary thermography catheter. A thermistor probe (Microchip NTC Thermistor, model 100K6-MCD368; BetaTHERM), 0.457 mm in diameter, is attached at the distal part of the thermography catheter (Epiphany, Medispes SW, Switzerland). The technical characteristics of the polyamide thermistor include *1*) temperature accuracy, 0.05°C; *2*) time constant, 300 ms; *3*) spatial resolution, 0.5 mm; and *4*) linear correlation of resistance versus temperature over the range of 33–43°C. The gold-plated lead wires of the thermistor pass through the shaft of the catheter and end in a connector at the distal part of the thermography catheter. At the distal 20 cm, the catheter has a second lumen for insertion of a guide wire; thus, the catheter can be inserted into the coronary artery over a standard guide wire (0.014 in). Opposite the thermistor is a hydrofoil specially designed to ensure contact of the thermistor on the vessel wall. The catheter is provided in sizes of 3.0–4.5 Fr.

The lesion of interest was well delineated in ≥2 views, on which the positioning of the catheter was based. The projections in which the lesion was best visualized were frozen for guidance of the thermography catheter advancement. Five minutes after the last injection of contrast medium, the coronary thermography catheter was advanced over the guidewire to the target vessel, and blood temperature was measured when the thermistor had just emerged from the tip of the guiding catheter without being in contact with the vessel wall. Thereafter, temperature was recorded at the proximal nondiseased segment, and the most frequent temperature was designated the proximal vessel wall temperature. Afterward, temperature recordings at the atherosclerotic lesion were performed based in the same projections, which were frozen from the initial angiography (Fig. 1). Temperature difference (ΔT) between the atherosclerotic plaque and the proximal vessel wall was calculated by subtracting the temperature at the proximal vessel wall from the maximal temperature at the lesion. After temperature measurements, the operator proceeded to the intervention.

Statistical analysis

Continuous variables are presented as means ± SD, while qualitative variables are presented as absolute and relative frequencies. The exact *P* values presented arise from nonparametric comparison (Wilcoxon test) and compared with a significant level of 5%. Moreover, parametric comparisons by the use of an unpaired *t* test were used to confirm the findings of nonparametric statistical analysis. STATA 6 software was used for the calculations (STATA, College Station, TX).

RESULTS

Study population

In the study, 108 patients were included and separated in two groups: 45 type 2 diabetic patients and 63 nondiabetic patients serving as a control group. Twenty-five patients with type 2 diabetes were treated by oral agents (55.6%), 15 were under hypoglycemic diet (33.3%), and 5 received a combination of insulin and oral agents (11.1%).

We also categorized the study population according to the clinical syndrome. Among patients with type 2 diabetes, 21 presented with acute coronary syndromes (ACSs) and 24 with chronic stable angina (CSA). In the control group, 22 patients with ACSs and 41 with CSA were enrolled. There were no differences between the two groups in the clinical and angiographic characteristics. The demographic and angiographic characteristics of the study population are demonstrated in Tables 1 and 2. All patients enrolled in the study underwent successful stent implantation without any complication.

Temperature measurements

In all patients, thermography was performed successfully without any complications. The measurement obtained for determination of the proximal vessel wall temperature was constant in each patient of the total study group, varying by only 0.03°C, with an SD from 0 to 0.03°C. The proximal vessel wall temperature and the temperature of the blood did not differ ($P = 0.7$).

Patients with type 2 diabetes had increased temperature difference compared with nondiabetic patients (mean ΔT: 0.17 ± 0.18°C vs. 0.09 ± 0.02°C, $P = 0.01$). Patients with type 2 diabetes showed increased thermal heterogeneity compared with nondiabetic patients in
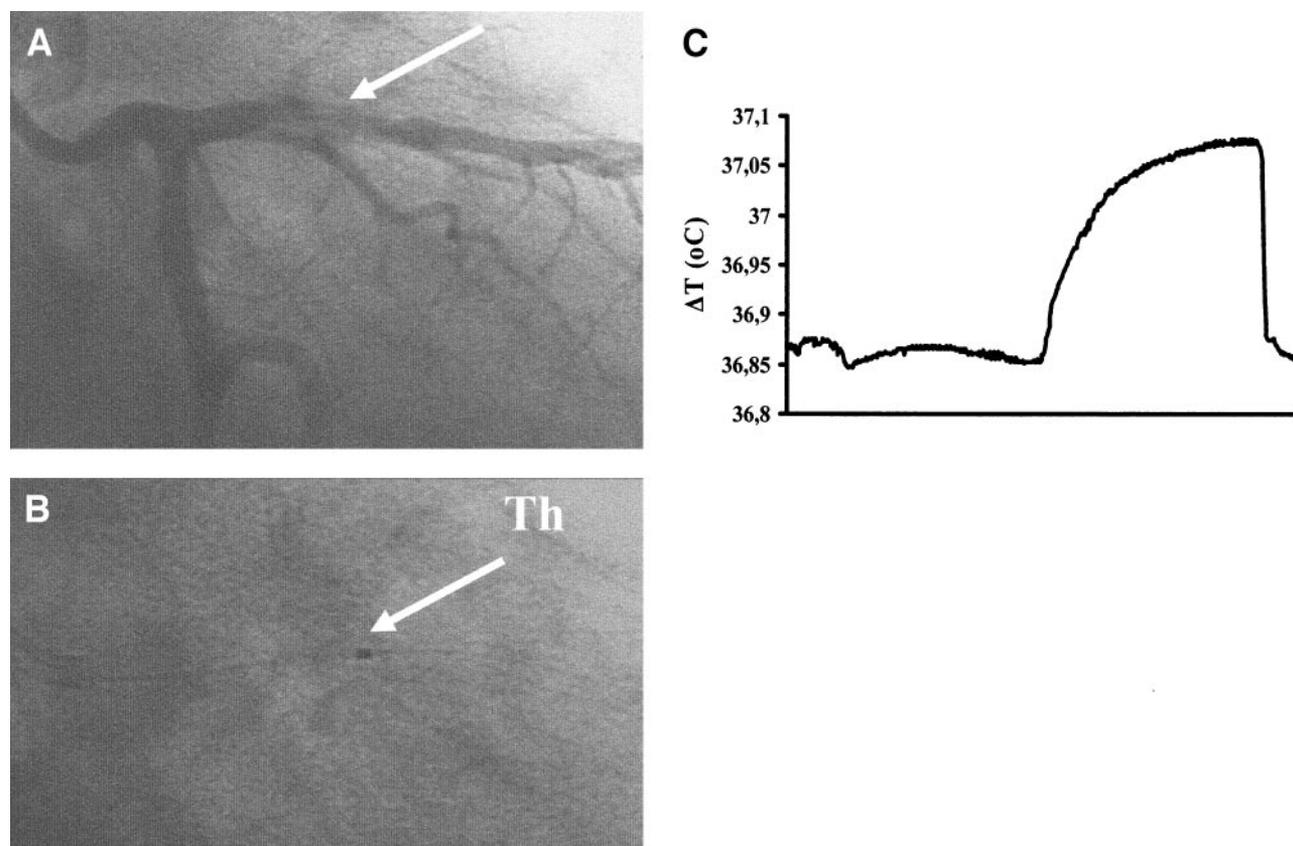
Figure 1—A*: The initial angiogram is demonstrated and a significant stenosis in the proximal segment of left anterior descending artery is revealed (arrow). B: The thermistor (Th) is shown at the site of the culprit lesion. C: The thermogram demonstrates a temperature difference (ΔT) between the atherosclerotic plaque temperature and the proximal vessel wall temperature of 0.10°C.*

the ACS group (mean ΔT: 0.29 ± 0.31°C vs. 0.15 ± 0.21°C, $P = 0.02$) and in the CSA group (mean ΔT: 0.09 ± 0.08°C vs. 0.05 ± 0.04°C, $P = 0.006$). Among patients with type 2 diabetes, those presenting with ACSs showed increased temperature difference compared with CSA (mean ΔT: 0.29 ± 0.31°C vs. 0.09 ± 0.08°C, $P = 0.007$), so were nondiabetic patients (mean ΔT: 0.15 ± 0.21°C vs. 0.05 ± 0.04°C, $P = 0.005$) (Fig. 2).

Twenty-three type 2 diabetic (47.6%) and 30 nondiabetic (51.1%) patients were under lipid-lowering therapy with statins for >4 weeks ($P = 0.72$). The distribution of statin agents among the treated patients was 34% atorvastatin, 34% pravastatin, 23% simvastatin, and 9% fluvastatin (mean therapy time: 4.2 ± 2.1 months).

All patients under statins had lower

Table 1—*Demographic characteristics stratified by diabetes and clinical syndrome*

	Nondiabetic	Diabetic	*P* value	ACS	CSA	*P* value
n	63	45		43	65	
Age (years)	60.67 ± 8.96	63.40 ± 9.32	0.13	59.98 ± 8.98	63.02 ± 9.16	0.09
Men	49 (77.8)	28 (62.2)	0.08	30 (69.8)	47 (72.3)	0.78
Hypertension	37 (58.7)	32 (71.1)	0.18	30 (69.8)	39 (60)	0.30
Smoking	36 (57.1)	21 (46.7)	0.28	27 (62.8)	30 (46.2)	0.09
Family history	23 (36.5)	9 (20)	0.06	13 (30.2)	19 (29.2)	0.91
Cholesterol (mg/dl)	205.10 ± 18.46	199.35 ± 15.46	0.11	202.60 ± 16.15	207.57 ± 18.51	0.95
LDL (mg/dl)	123.76 ± 17.92	118.71 ± 15.13	0.13	124.60 ± 18.03	120.74 ± 15.23	0.96
Fasting glucose (mg/dl)	102.94 ± 9.89	122.04 ± 15.51	<0.01	114.51 ± 19.82	108.51 ± 11.73	0.051
Statins	30 (47.6)	23 (51.1)	0.72	18 (41.9)	35 (53.8)	0.22
ACE inhibitors	19 (30.2)	21 (46.7)	0.08	17 (39.5)	23 (35.4)	0.66
Aspirin	52 (82.5)	39 (86.7)	0.56	37 (86)	54 (83.1)	0.18
β-Blocker	42 (66.7)	28 (62.2)	0.63	34 (79.1)	36 (55.4)	0.13

Data are means ± SD or *n* (%).

Table 2—*Angiographic characteristics stratified by diabetes and clinical syndrome*

	Nondiabetic	Diabetic	*P* value	ACS	CSA	*P* value
n	63	45		43	65	
Vessels						
Left anterior descending artery	21 (33.3)	14 (31.1)		15 (34.9)	20 (30.8)	
Left circumflex artery	19 (30.2)	13 (28.9)	0.96	8 (18.6)	23 (35.4)	0.15
Right coronary artery	24 (38.1)	18 (40.0)		20 (46.5)	22 (33.8)	
Location						
Proximal	19 (30.2)	16 (35.6)		9 (20.9)	26 (40)	
Middle	36 (57.1)	19 (42.2)	0.25	25 (58.2)	30 (46.2)	0.10
Distal	8 (12.7)	10 (22.2)		9 (20.9)	9 (13.8)	
Reference vessel diameter (mm)	2.86 ± 0.41	2.81 ± 0.70	0.72	2.80 ± 0.60	2.86 ± 0.51	0.68
Pre–minimal lumen diameter (mm)	0.85 ± 0.45	0.71 ± 0.49	0.23	0.73 ± 0.48	0.83 ± 0.46	0.47
Length (mm)	13.58 ± 5.40	12.09 ± 3.65	0.24	14.79 ± 5.62	12.33 ± 4.37	0.07
Stenosis (%)	69.12 ± 13.15	74.18 ± 15.79	0.17	71.30 ± 16.19	70.91 ± 13.67	0.92

Data are means ± SD or *n* (%).

thermal heterogeneity compared with untreated patients (mean ΔT: 0.07 ± 0.09°C vs. 0.17 ± 0.20°C, $P = 0.003$). Patients with type 2 diabetes under statins had lower thermal heterogeneity compared with untreated patients with type 2 diabetes (mean ΔT: 0.11 ± 0.12°C vs. 0.22 ± 0.21°C, $P = 0.02$). Nondiabetic patients under statins also had lower thermal heterogeneity compared with untreated patients (mean ΔT: 0.05 ± 0.04°C vs. 0.13 ± 0.18°C, $P = 0.01$) (Fig. 2).

There was no interaction, however, between statins intake and clinical syndrome with temperature difference ($P = 0.42$). There was no correlation between the levels of LDL and temperature difference ($P = 0.33$). The correlation between the glucose levels with temperature difference did not reach statistical significance ($P = 0.12$).

CONCLUSIONS — The main findings of the present study are that *1*) there is profound thermal heterogeneity in culprit lesions of type 2 diabetic compared with nondiabetic patients with CAD, *2*) the clinical syndrome has an impact on plaque temperature of patients with type 2 diabetes, as in ACS heat production is increased, and *3*) statin administration has a favorable effect on plaque temperature of patients with type 2 diabetes.

Inflammation is closely related to type 2 diabetes, as insulin resistance and hyperglycemia have proinflammatory effects. Recent studies (10,11) demonstrated that chronic subclinical inflammation is associated with insulin resistance and comprises a component of the metabolic syndrome with further unfavorable effects on atherosclerosis. Moreover, hyperglycemia is also an important predictor for plasma C-reactive protein in nondiabetic subjects (12). Especially in patients with type 2 diabetes with CAD, an increased inflammatory activation is observed compared with nondiabetic patients (1,13–16). The concentration of other inflammatory markers is also greater in patients with diabetes with or without overt CAD than in control subjects (1). These studies demonstrate that widespread inflammation is observed in the presence of diabetes. Moreover, local inflammatory activation has been reported in coronary atherosclerotic plaques of patients with diabetes. Histological examination of coronary tissue from patients with diabetes exhibits a larger content of lipid-rich atheroma and macrophage infiltration compared with nondiabetic patients (14–16). In agreement with these observations, we found an increased local thermal heterogeneity
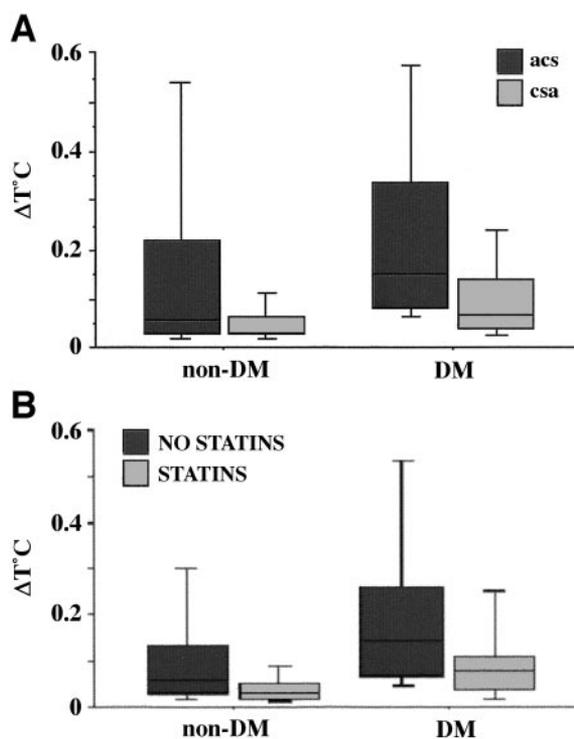

Figure 2—A*: The difference (ΔT) in atherosclerotic plaque temperature from proximal vessel wall temperature in type 2 diabetic and nondiabetic patients stratified by the clinical syndrome is presented. B: Temperature difference (ΔT) in type 2 diabetic and nondiabetic patients stratified by statins intake is presented. The bottom of the box represents the first quartile, the top of the box represents the third quartile, and the line in the box represents the median value.*

in culprit atherosclerotic plaques of patients with diabetes. Animal studies (6) and human observations (4,8) confirmed that local heat generation is associated with increased macrophage content. Thus, our results may be explained from the greater inflammatory cell infiltration within the culprit lesions of patients with diabetes.

In patients with ACSs an increased inflammatory activation is observed (17) with accompanied increased local atherosclerotic plaque temperature (3). The inflammatory activation is even greater in patients with diabetes suffering from ACSs, as angioscopy ulcerated plaques are more frequently found in diabetic patients with associated intracoronary thrombi (18). Atherectomy specimens from coronary atherosclerotic plaques of patients with unstable angina also demonstrated that the percentages of total area occupied by lipid-rich atheroma and macrophages were larger in specimens from patients with diabetes (14). These observations may explain the findings of the present study, in which patients with ACSs and diabetes had higher temperature of the culprit atherosclerotic plaques compared with patients with CSA and diabetes. The increased local inflammatory activation, demonstrated in the present study by a greater heat production, may have a significant impact on the clinical outcome of diabetic patients suffering from ACSs. Indeed previous studies indicated that this group of patients has the worse clinical outcome compared with nondiabetic patients, as diabetic patients have a higher overall incidence of death or reinfarction at long-term follow-up (19).

Another finding of the current study was the favorable effect of statins on atherosclerotic plaque temperature of patients with diabetes. Previous studies (6,9,20) have shown that hypolipidemic diet or statin administration is associated with lower heat generation from atherosclerotic plaques. The possible mechanism is the reduction of macrophage content of atherosclerotic plaque due to the pleiotropic effect of statins. In the present study, this favorable effect was also found in patients with diabetes, independently of the levels of LDL. Interestingly, temperature difference of patients with diabetes receiving statins was similar to untreated nondiabetic patients. We may postulate that the favorable effect of statin seems to be more potent in patients

with diabetes. Recent studies are provocative regarding the issue of statin administration in people with diabetes for reducing the risk of cardiovascular disease events independently of LDL cholesterol levels (21).

Study limitations
Despite the relative small sample size, the results of the study clearly demonstrate the increased local inflammatory activation in the culprit lesions of patients with diabetes and the favorable effect of statins on heat generation from atheromatic plaques. In this study, we included patients with significant lesions (Table 2). We cannot extrapolate the current results in intermediate lesions, in which the "cooling effect" of coronary blood flow has significant effect on coronary thermography measurements. However, we used different catheters depending on the percentage of stenosis and the size of the vessel to avoid the cooling effect of coronary blood flow on coronary thermography. Although thrombotic material may contribute to the heat generation from culprit lesions of patients with ACSs, previous observations demonstrated that temperature measurements before and after predilatation with balloon, by which thrombus is dissolved, are not influenced (3).

We focused on the effect of type 2 diabetes on local heat generation. The severity of diabetes, as assessed by the HbA_{1c} (A1C) levels, on heat generation from atherosclerotic plaque needs to be investigated in other studies.

In conclusion, the results of the present study reveal that local heat generation is increased in culprit significant lesions of type 2 diabetic compared with nondiabetic patients. Statin treatment also has a favorable effect on plaque temperature in patients with diabetes.

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