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Elevated Plaque Temperature in Non-Culprit De Novo Atheromatous Lesions of Patients With Acute Coronary Syndromes

Konstantinos Toutouzas, MD, Maria Drakopoulou, MD, John Mitropoulos, MD, Eleftherios Tsiamis, MD, Sophia Vaina, MD, Manolis Vavuranakis, MD, Virginia Markou, MD, Eirini Bosinakou, MD, Christodoulos Stefanadis, MD, FACC, FESC

Athens, Greece

OBJECTIVES We investigated whether there is increased temperature in non-culprit lesions, and the correlation of clinical syndrome with heat production of non-culprit lesions.

BACKGROUND There is a controversy regarding whether there is widespread inflammation involving non-culprit lesions, or whether inflammatory involvement is limited to the culprit lesion. Coronary thermography assesses the local inflammatory involvement in atherosclerotic lesions.

METHODS We included patients suffering from stable angina (SA) or acute coronary syndrome (ACS). All patients had two or more angiographically detectable lesions at different arteries. Culprit lesions should be identified in all patients. Patients with chronic total occlusions and multiple significant lesions at the culprit vessel were excluded. We measured at each non-culprit lesion the temperature difference (ΔT) between the atherosclerotic plaque and the proximal vessel wall temperature.

RESULTS The study population included 42 patients: 23 with SA, 19 with ACS. The ΔT in non-culprit lesions was $0.08 \pm 0.07^{\circ}C$. Patients with ACS had a higher temperature difference in non-culprit lesions compared with patients with SA (ACS $0.11 \pm 0.08^{\circ}C$ vs. SA $0.05 \pm 0.06^{\circ}C$; $p < 0.01$). The mean value of ΔT in non-culprit lesions was higher in the untreated group compared with the treated group with statins ($0.11 \pm 0.10^{\circ}C$ vs. $0.06 \pm 0.05^{\circ}C$; $p = 0.05$).

CONCLUSIONS The results of this study show that heat is generated in non-culprit lesions. Moreover, in patients with ACS, temperature difference is increased compared with patients with stable angina. (J Am Coll Cardiol 2006;47:301–6) © 2006 by the American College of Cardiology Foundation

There is a controversy regarding whether in patients with acute coronary syndrome (ACS) there is diffuse destabilization of atherosclerotic plaques or only the culprit lesion is characterized as vulnerable plaque. Several studies have shown that non-culprit lesions are destabilized because they have similar morphologic characteristics with culprit lesions detected by angiography, intravascular ultrasound, and angioscopy (1–4). These studies support that there is a diffuse destabilization of atherosclerotic plaques, leading to the concept that plaque instability may not represent a mere random vascular accident, but reflect a pan-coronary process because of widespread inflammatory activation, as shown by measuring systemic inflammatory indexes (5–7). However, other studies by intravascular ultrasound have shown that culprit lesions of patients with ACS have local morphologic characteristics distinct from non-culprit lesions (8–10).

Coronary thermography is a method for functional assessment of atherosclerotic plaques. Marked temperature elevation is shown in culprit atherosclerotic lesions. Several ex vivo and in vivo studies have shown a correlation between inflammatory involvement and heat production in atherosclerotic plaques (11–15). The first ex-vivo study showed increased heat production in human atherosclerotic plaques and a positive correlation between the concentration of macrophages and plaque temperature (11). In vivo studies showed that in patients with coronary artery disease a temperature increase is observed, progressively increasing from patients with chronic stable angina (SA) to patients with ACS (16). Moreover, the anti-inflammatory effect of either dietary cholesterol lowering or administration of statins was shown to be associated with reduction of local temperature in animals and humans (13,17).

There are no reports, however, regarding the prevalence of temperature differences in the non-culprit lesions and whether heat production from non-culprit lesions is associated with clinical syndromes of coronary artery disease. Thus, the goal of this study was to investigate whether there is: 1) an increase in temperature in non-culprit lesions, and 2) a correlation between clinical syndrome and local plaque temperature measurements.

METHODS

Study population. We included consecutive patients with SA or ACS with de novo non-culprit atherosclerotic lesions

From the Hippokration Hospital, First Department of Cardiology, Athens Medical School, Athens, Greece.

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Abbreviations and Acronyms
ACS = acute coronary syndrome
SA = stable angina
ΔT = temperature difference

that were subjected to percutaneous coronary intervention for the treatment of the culprit lesion. Angiographic inclusion criteria were: at least one angiographic non-culprit lesion, <20 mm in length, producing an intermediate stenosis (50% to 75%) in vessels with a reference diameter ≥2.25 mm. The non-culprit lesion had to be clearly identified from the culprit lesion by the combination of pre-crisis and inter-crisis electrocardiographic findings, left ventricular wall motion abnormalities, scintigraphic defects, and angiographic lesion morphology. Two experienced cardiologists (E.T. and M.V.) independently reviewed all clinical and angiographic data to decide angina status and culprit lesions before the procedure. In the case of disagreement, the patient was excluded from the study.

We excluded patients medicated with corticosteroids or nonsteroidal anti-inflammatory drugs, except for aspirin. In addition, patients with an intercurrent inflammatory or neoplastic condition likely to be associated with an acute-phase response were not enrolled in the study. Patients with chronic total occlusion, inability to detect the non-culprit lesion, or procedure failure or complication during the treatment of the culprit lesion were excluded from the study. The institutional ethics committee approved the study protocol, and each patient provided written informed consent.

Clinical demographics. Risk factors included diabetes mellitus, hypertension, hypercholesterolemia, and current smoking; SA was no change in frequency, duration, or intensity of symptoms within six weeks; ACS included patients with unstable angina and acute myocardial infarction. Unstable angina was new-onset severe angina, accelerated angina, or rest angina. New-onset angina was considered angina of <2 months in duration, and accelerated angina was considered angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously. Previous myocardial infarction (<6 weeks), coronary artery bypass grafting, percutaneous coronary intervention in other lesions, and left ventricular function were tabulated.

Angiographic analysis. Coronary angiograms were analyzed with a computer-assisted, automated edge detection algorithm (Medcon, Tel Aviv, Israel) by a core laboratory 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. At the distal part of the thermography catheter, a thermistor is positioned. The technical characteristics of the thermistor have been previously described (16–18). Briefly, the temperature accuracy is 0.05°C and the time constant is 300 ms. The coronary thermography catheter (Epiphany, Medispes S.W., Zug, Switzerland) contains two lumens. The first lumen runs through the distal 20 cm of the device and is used for insertion of a guidewire (0.014 inches). The guidewire is advanced by a monorail system. In the second lumen, the thermistor leads are inserted. The catheter is provided in sizes from 3-F to 4.5-F.

PROCEDURE. The lesion of interest was well delineated in two or more views, on which the positioning of the catheter was based. 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 non-diseased segment and the most frequent temperature was designated the proximal vessel wall temperature. Afterward, temperature recordings at the atherosclerotic non-culprit lesion were performed. 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 non-culprit lesion. Significant temperature difference was assigned $\Delta T \geq 0.05$°C based on the technical characteristics of the thermistor used in the thermography catheter (14–16). The operators had no knowledge of the temperature measurements. The technician operators of the thermography equipment recorded the temperature at the non-culprit lesion (18), and the analysis of the results was preformed blindly by M.D. and J.M. The treatment of the lesions was at the operator's discretion.

Statistical analysis. Continuous variables are presented as mean ± one standard deviation as well as median because of their skewed distribution. Categorical variables are presented as absolute and relative frequencies. The presented figures show median and interquartile range (box plots) because of the skewed distribution of ΔT.

To evaluate the independent effect of clinical syndrome and statins on ΔT, we initially performed an explanatory analysis based on non-parametric procedures. In particular, Spearman correlation coefficients and Mann-Whitney criteria were applied to evaluate the associations between ΔT and clinical syndrome, treatment group (statin or not), age, gender, treated vessel, diabetes mellitus, smoking status, hypertension, family history of premature coronary artery disease, reference diameter, minimal lumen diameter, aspirin, beta blockers, and angiotensin-converting enzyme inhibitors.

Then we performed multiple regression analysis using log-ΔT as the dependent outcome and the aforementioned factors as explanatory variables. We have log-transformed

Table 1. Demographic Characteristics

	n = 42
Age, yrs	61.78 ± 10.40
Male	30 (71.4)
Ejection fraction, %	49.27 ± 7.67
Hypertension	28 (66.6)
Diabetes mellitus	13 (30.9)
Family history	10 (23.8)
Current smoker	23 (54.8)
Cholesterol	32 (76.2)
Statin	29 (69.1)
Aspirin	38 (90.5)
Angiotensin-converting enzyme inhibitors	19 (45.2)
Beta-blockers	27 (64.3)

Values are mean ± SD or n (%)

ΔT to fulfill the assumption of normality for the standardized residuals of the regression model.

The exact p values presented arise from non-parametric comparison and were compared with a significance level of 5%. The STATA 6 software package was used for the calculations (STATA Corp., College Station, Texas).

RESULTS

Study population. Between November 2002 and December 2004, a total of 42 consecutive patients fulfilled the criteria and were included in the study. During the same period, 136 patients with two-vessel disease were excluded from the study because the majority did not fulfill the angiographic inclusion criteria. Additional reasons for exclusion from the study were patient refusal, inability to identify or disagreement on the identification of the culprit lesion, and failure or complications during the treatment of the culprit lesion.

Of the 42 patients finally included, 19 patients had ACS and 23 patients had SA. The demographic characteristics are shown in Table 1. Five patients were treated with glycoprotein IIb/IIIa receptor blocker agents during the procedure. The treatment of culprit and non-culprit lesions was left to the discretion of the operator. The majority (n = 27, 64.3%) of the non-culprit lesions were treated by successful stent implantation.

Table 2. Angiographic Characteristics

	Non-Culprit Lesions (n = 42)
Vessels	
LAD	7 (16.6)
LCX	19 (45.2)
RCA	16 (38.0)
Location	
Proximal	11 (26.2)
Middle	22 (52.4)
Distal	9 (21.4)
RD (mm)	2.74 ± 0.48
Pre-MLD (mm)	0.75 ± 0.36
Length (mm)	13.87 ± 6.6
Stenosis (%)	65.86 ± 10.05

Values are n (%) or mean ± SD.
LAD = left anterior descending artery; LCX = left circumflex artery; MLD = minimal lumen diameter; RCA = right coronary artery; RD = reference diameter.

Table 3. Demographic Characteristics Stratified by the Clinical Syndrome

	Acute Coronary Syndrome (n = 19)	Stable Angina (n = 23)	p Value
Age, yrs	61.31 ± 9.02	62.17 ± 11.60	0.79
Male	13 (68.4)	17 (73.9)	0.74
Ejection fraction (%)	48.95 ± 10.08	49.56 ± 5.14	0.79
Hypertension	13 (68.4)	15 (65.2)	0.99
Diabetes mellitus	6 (31.6)	7 (30.4)	0.93
Hypercholesterolemia	16 (84.2)	16 (69.5)	0.30
Statin	11 (57.8)	18 (78.3)	0.19
Aspirin	18 (94.7)	20 (86.9)	0.61
Angiotensin-converting enzyme inhibitors	8 (42.1)	11 (47.8)	0.76
Beta-blockers	12 (63.1)	15 (65.2)	0.99
Family history	4 (21)	6 (26)	0.70
Current smoking	13 (68.4)	10 (43.5)	0.13

Values are mean ± SD or n (%).

The angiographic characteristics of non-culprit lesions are shown in Table 2. We also categorized the study population according to the clinical syndrome. The demographic and angiographic characteristics of patients suffering from ACS or SA are shown in Tables 3 and 4, respectively.

Temperature measurements. The measurements obtained for determination of background temperature were constant in each patient of the total study group, varying by only 0.03°C, with a standard deviation from 0 to 0.03. The background temperature and the temperature of the blood did not differ (p = 0.5). In all non-culprit lesions, thermography was performed successfully without any complications. Non-culprit lesions had a mean value temperature difference 0.08 ± 0.07°C. Twenty-three patients (54.8%) had a significant temperature elevation in non-culprit lesions. The mean percentage of stenosis in non-culprit lesions with increased temperature was 67.93 ± 10.26% and in lesions with ΔT <0.05°C was 63.36 ± 9.45% (p = 0.15).

Table 4. Angiographic Findings Stratified by the Clinical Syndrome

	Acute Coronary Syndrome (n = 19)	Stable Angina (n = 23)	p Value
Vessels			
LAD	2 (10.5)	5 (21.7)	
LCX	10 (52.6)	9 (39.1)	0.54
RCA	7 (36.8)	9 (39.1)	
Location			
Proximal	6 (31.6)	5 (21.7)	
Middle	8 (42.1)	14 (60.9)	0.47
Distal	5 (26.3)	4 (17.4)	
RD (mm)	2.58 ± 0.36	2.87 ± 0.54	0.06
Pre-MLD (mm)	0.84 ± 0.26	1.02 ± 0.40	0.12
Length (mm)	12.01 ± 3.50	13.23 ± 7.45	0.64
Stenosis (%)	67.30 ± 9.73	64.80 ± 10.81	0.45

Values are n (%) or mean ± SD.
Abbreviations as in Table 2.

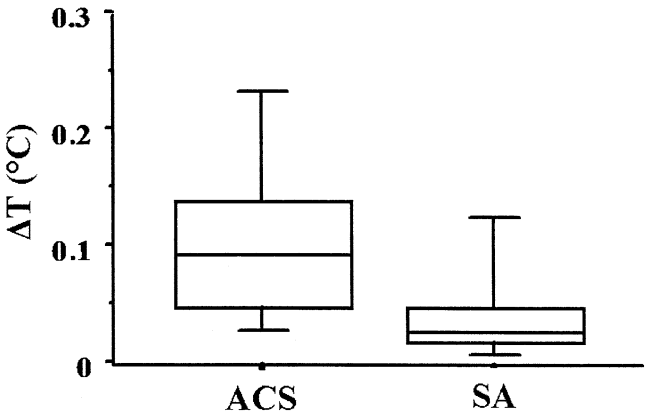

Figure 1. The difference in atherosclerotic plaque temperature from proximal vessel wall temperature (ΔT) in non-culprit lesions in patients with acute coronary syndromes (ACS) and stable angina (SA). The **bottom of the box** represents the first quartile, the **top of the box** represents the third quartile, and the **line in the box** represents the median value.

There was no significant correlation between mean lumen distance and ΔT ($p = 0.37$).

When analyzed by the type of clinical syndrome, patients with ACS had higher ΔT values compared with patients with SA (ACS 0.11 ± 0.08°C vs. SA 0.05 ± 0.06°C; $p < 0.01$) (Fig. 1, Table 5). The percentage of lesions with elevated temperature in patients with ACS was 84.2% (16 of 19 lesions) and in patients with SA was 30.4% (7 of 23 lesions) ($p < 0.001$). Of the total study population, 29 patients received statins ≥4 weeks and 13 were not under statin treatment. The mean value of ΔT in non-culprit lesions was higher in the untreated group compared with the group treated with statins (0.11 ± 0.10°C vs. 0.06 ± 0.05°C; $p = 0.05$) (Fig. 2).

Multiple linear regression analysis confirmed that patients with ACS had higher ΔT compared with patients with SA (b ± standard error, 0.04 ± 0.02, $p = 0.02$). Statin intake was also a predictor for ΔT, although statistical significance was not achieved in this model ($p = 0.18$).

DISCUSSION

The main findings of the present study are that non-culprit intermediate lesions have an increased temperature difference, and non-culprit lesions of patients with ACS have significantly higher ΔT compared with lesions of patients with chronic SA. Moreover, statins seem to have a favorable effect on heat generation from non-culprit lesions.

This study provides information regarding the functional assessment of non-culprit lesions. Current studies provide conflicting results regarding the morphologic characteristics of non-culprit lesions. The widespread vulnerability of both culprit and non-culprit lesions has been shown by several studies using multiple methods (1–4,6,19). The use of intravascular ultrasound has provided significant information regarding this issue. Intravascular ultrasound examination has shown multiple plaque ruptures in patients with varying clinical presentations (3). Especially in patients with ACS, thrombi and multiple ruptures were more common and usually did not cause lumen compromise. These results were confirmed by three-vessel intravascular ultrasound examination, because multiple plaque ruptures were more common in patients with acute myocardial infarction compared with patients with SA (20). These results were also confirmed by angioscopy and recently by optical coherence tomography (4,21). Moreover, the widespread instability of atherosclerotic plaques extends also in carotid arteries, because patients with unstable angina have morphologic characteristics of instability in carotid artery plaques (22). All of these studies challenge the concept of a single vulnerable plaque in unstable coronary syndromes.

Other studies, however, support the idea that culprit plaques have distinct morphologic characteristics from non-culprit plaques and that the vascular event is determined by

Table 5. Individual Data of the Study Population

No.	Clinical Syndrome	ΔT (°C)
1	SA	0.02
2	ACS	0.10
3	ACS	0.05
4	SA	0.02
5	SA	0.02
6	SA	0.05
7	SA	0.04
8	SA	0.02
9	ACS	0.03
10	SA	0.06
11	ACS	0.10
12	SA	0.02
13	ACS	0.09
14	ACS	0.09
15	ACS	0.25
16	SA	0.01
17	SA	0.21
18	SA	0.01
19	ACS	0.05
20	SA	0.01
21	SA	0.20
22	ACS	0.08
23	ACS	0.14
24	SA	0.03
25	SA	0.03
26	ACS	0.16
27	ACS	0.10
28	ACS	0.05
29	SA	0.03
30	SA	0.05
31	ACS	0.07
32	ACS	0.14
33	ACS	0.29
34	ACS	0.02
35	SA	0.04
36	SA	0.02
37	ACS	0.02
38	ACS	0.20
39	SA	0.09
40	SA	0.07
41	SA	0.01
42	SA	0.04

ACS = acute coronary syndrome; SA = stable angina.

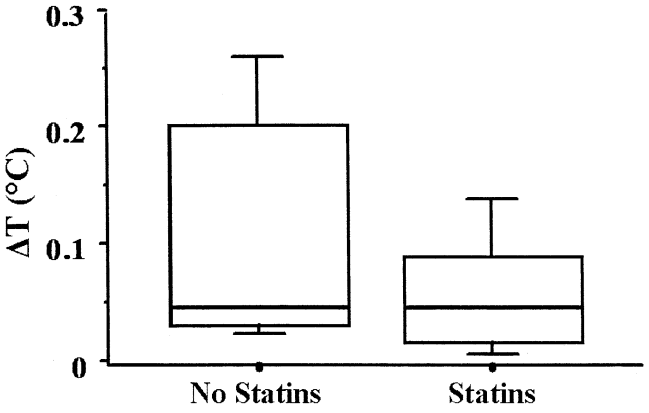

Figure 2. The difference in atherosclerotic plaque temperature from proximal vessel wall temperature (ΔT) in non-culprit lesions in untreated patients and in patients under statin treatment. The **bottom of the box** represents the first quartile, the **top of the box** represents the third quartile, and the **line in the box** represents the median value

pre-event morphologies. Hoffmann et al. (10) have shown that local factors tend to be more important than patient factors in determining the lesion morphology. Intravascular ultrasound examination has shown that culprit plaques have more markers of instability (8–9).

Despite the large amount of information regarding the morphologic characteristics of remote lesions, we lack studies with functional assessment of non-culprit lesions. We showed for the first time by coronary thermography, at least to our knowledge, that non-culprit lesions have a temperature difference. It has been shown previously that culprit lesions produce heat, which can be detected in vivo by several catheter designs (16,23–26). This finding has been associated with the local and systemic inflammatory status in experimental and clinical studies (12,13,27–29). We evaluated local temperature differences in intermediate non-culprit lesions, and the results of the current study show that heat is also generated in atheromatous plaques, which are not related by protocol to the clinical syndrome of the study population. Moreover, in patients with ACS, a temperature increase is observed in non-culprit lesions, supporting a pan-coronary inflammatory activation. We cannot draw safe conclusions regarding the etiology of elevated temperature in non-culprit lesions found in patients with ACS. It seems, however, that the increased temperature found in the non-culprit lesions of patients with ACS is not a secondary phenomenon, because in patients with chronic SA (30%) elevated temperature was also found. Another observation supporting this concept is the prolonged temperature elevations in culprit lesions observed in patients investigated after the acute phase of myocardial infarction (15).

The findings of the present study suggest that statin administration seems to have a beneficial effect on non-culprit lesion temperature difference. Previous studies have shown that statin administration is associated with reduced heat generation from culprit lesions (17). The results of this study support that the pleiotropic effects of statins are implicated also in non-culprit atheromatic plaques. This concept, however, needs to be confirmed in studies with a larger number of patients.

Study limitations. Although the study group was rather small, the conclusions of the study are supported by our findings. Non-culprit lesions were angiographically intermediate, and therefore the conclusions cannot be extrapolated to stenoses <50% or in significant lesions. However, the treatment of lesions provoking significant stenosis is not the major problem in the clinical practice, because intervention is usually performed. Intermediate stenoses need to be further evaluated, morphologically and functionally, because the decision for intervention is not always clear. Stenoses <50% are also important and should be evaluated for prevention of future ACS. However, the coronary thermography catheter used in the current study cannot exclude the cooling effect of blood flow (30–33), and therefore safe conclusions cannot be drawn in low-grade stenoses. In the present study, a trend toward larger minimal lumen diameter was observed in patients with SA compared with patients with ACS. However, there was no correlation between minimal lumen diameter and ΔT. Finally, regarding the issue of collection of temperature recordings, the operators had no knowledge of the temperature measurements, because these were performed by technician operators, and the analysis of temperature differences was performed blindly.

Although the favorable effect of statins was shown in this study, in the multivariate analysis statistical significance was not achieved. However, we must mention that the effect of statins in this study population was not the primary target of the current study and a post hoc analysis was performed.

CONCLUSIONS

Non-culprit intermediate lesions have temperature difference that is increased in patients with angiotensin-converting enzyme. The results of this study support the concept of global coronary instability. Moreover, statins seem to have a favorable effect on heat generation from non-culprit lesions.

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Reprint requests and correspondence: Dr. Konstantinos Toutouzas, 24 Karaoli and Dimitriou str., 15562 Holargos, Athens, Greece. E-mail: ktoutouz@otenet.gr.

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