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Statin treatment is associated with reduced thermal heterogeneity in human atherosclerotic plaques

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Aims Heat released from atherosclerotic plaques as a result of the local inflammatory process, may be measured in vivo by a thermography catheter. Statins seem to have an antiinflammatory effect which results in plaque stabilization. The aim of this study was to investigate the effect of statins on plaque temperature.

Methods and Results The study population included 72 patients: 21 with effort angina, 32 with unstable angina and 19 with acute myocardial infarction. In the study group, 37 patients received statins for more than 4 weeks and 35 were not receiving statins. We measured the temperature difference (ΔT) between the atherosclerotic plaque and the proximal vessel wall (background temperature) using a thermography catheter. The statistical analysis showed that the mean value of ΔT was higher in the untreated group compared to the treated-with-statin, group ($0{\cdot}56 \pm 0{\cdot}41$ vs $0{\cdot}29 \pm 0{\cdot}33$ °C, $P<0{\cdot}01$). Moreover, a progressive increase in ΔT by type of clinical syndrome was observed in both groups (statin group; effort angina: $0{\cdot}24 \pm 0{\cdot}15$, unstable angina: $0{\cdot}26 \pm 0{\cdot}26$, acute myocardial infarction: $0{\cdot}40 \pm 0{\cdot}28$, vs untreated group; effort angina: $0{\cdot}41 \pm 0{\cdot}26$, unstable angina: $0{\cdot}44 \pm 0{\cdot}28$, acute myocardial infarction: $0{\cdot}84 \pm 0{\cdot}52$, $P<0{\cdot}05$). Multivariate analysis showed that treatment with statins was an independent factor in temperature variation, after taking into account the effect of the clinical syndrome ($P<0{\cdot}05$).

Conclusions Patients on statin treatment produce less heat from the culprit coronary lesion than those not treated. Thus, statins seem to have a favourable effect on heat release from atherosclerotic plaques, and whether this effect has an impact on plaque stabilization needs to be investigated in future studies.
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Introduction

Recent trials have demonstrated that treatment with lipid-lowering drugs and especially with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) is associated with reduced cardiovascular events and mortality[1–5]. Previous angiographic studies revealed that lipid-lowering therapy is associated with less progression, more regression and less new lesion development[6–9]. The benefit of statins, however, on cardiovascular end-points and coronary stenosis is incompletely explained by the treated cholesterol level. Treatment with statins may involve non-lipid mechanisms that modify endothelial function, smooth muscle cells, and monocyte–macrophage interactions, vasomotor function, inflammatory responses, and plaque stability. Accordingly, statins exert their cardiovascular benefits through direct antiatherogenic properties in the arterial wall and 'stabilization' of the plaque, beyond their effects on plasma lipids[10–13].

Recent ex vivo and in vivo studies have revealed that thermal heterogeneity is observed in the majority of unstable plaques[14–19]. Casscells *et al.* showed that heat is released by activated inflammatory cells in the atherosclerotic plaques of human carotid arteries[14]. Thermography is used to measure temperature changes within the atherosclerotic plaque in human coronary and peripheral arteries[15–17]. Furthermore, increased plaque temperature associated with acute-phase reactants is an expression of aggressive inflammation[18]. The impact of statins on inflammatory markers has been demonstrated in several studies[10–13, 20–23].

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However, the effect of statins on atherosclerotic plaque temperature is unknown. The aim of this study was to investigate the association between the temperature of atherosclerotic plaques and the administration of statins.

Methods

Study group

From December 1997 to June 2001, 122 patients underwent coronary thermography in the Department of Cardiology of Athens Medical School. Inclusion criteria involved the presence of a single lesion <20 mm in length in a major native coronary artery with a proximal reference vessel diameter ≥2·5 mm. The clinical definition criteria were based on the report of the patient and current medication. In order to eliminate the potentially, confounding effect of a clinical syndrome on the evaluation of temperature measurements, we applied a stratified randomization procedure[24]. In particular, we randomly selected 35 patients who were treated with statins for over 4 weeks. Then we observed the prevalence of a clinical syndrome (strata) in the mentioned group. Based on the observed prevalence of the clinical syndrome in the treated group we randomly selected 37 untreated patients (using the same procedure described above). Thus, the distribution of a major characteristic of our patients (i.e. the type of syndrome) was balanced, both in the treated and the untreated groups, and its potentially, confounding effect was limited. According to this design, the study population consisted of 72 patients. Twenty-one patients had effort angina, 32 presented with unstable angina unresponsive to maximal medical treatment after a 2-day hospital period, and 19 with an acute myocardial infarction for which primary angioplasty was performed within 6 h after the onset of pain.

Patients medicated with corticosteroids or non-steroidal antiinflammatory drugs, except for aspirin, were excluded from the study. Moreover, patients with an intercurrent inflammatory or neoplastic condition likely to be associated with an acute-phase response were not enrolled in the study. Finally, patients with multivessel disease and previous myocardial infarction during the last month were excluded from the study. In all patients, percutaneous revascularization was performed. The Institutional Ethics Committee approved the study protocol, and each patient provided written, informed consent.

Temperature measurements

Thermistor

A thermistor probe (Microchip NTC Thermistor, model 100K6MCD368, BetaTHERM, Ireland) was used for temperature measurements. The technical characteristics of the polyamide thermistor included: (i) temperature accuracy of 0·05 °C, (ii) a time constant of 300 ms, (iii) spatial resolution of 0·5 mm, and (iv) linear correlation of resistance vs temperature over the range of 33–43 °C[15–19].

Data acquisition and processing

The thermistor leads were connected to a digital multimeter (Protek 506) with an RS232C interface. The multimeter was connected to a personal computer (200-MHz Intel Pentium) and the resistance is displayed on real-time. Resistance changes were correlated with temperature changes according to the Steinhart–Hart equation. Finally, after the conversion of resistance values to temperature values (by Microsoft Excel) the temperature changes were demonstrated on the screen of the personal computer. All data were stored in the computer.

Coronary thermography catheter

The coronary thermography catheter (Medispes S.W., ZUG, Switzerland) has been described in detail in previous reports. Briefly, the catheter is 3F in diameter and contains a second lumen, which runs through its distal 20 cm and is used for insertion of a guidewire (0·014 in). The thermistor is attached to the distal part of the catheter. Opposite the thermistor is a hydrofoil specially designed to ensure contact by the thermistor to the vessel wall under flow (thickness of the catheter at this site, 4F). The catheter is advanced to the target lesion by a monorail system[15–19].

Procedure

After insertion of a guiding catheter, quantitative coronary angiography was performed. The lesion of interest was outlined in ≥2 well-opacified views with biplane angiography, on which the positioning of the catheter was based. The coronary thermography catheter was then advanced through the guiding-catheter 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, five temperature measurements over a length of approximately 1 cm of normal vessel wall proximal to the lesion were performed. All measurements were performed 5 min after the last injection of contrast medium. The most frequent temperature of these locations was designated as background temperature[15–19]. In cases in which the measurements for determination of background temperature were not constant, varying by >0·05 °C, repeat measurements were performed in a healthy vessel wall confirmed by intravascular ultrasound.

Afterwards, five measurements at the atherosclerotic lesion were performed. Accordingly, the difference in temperature (ΔT) between the atherosclerotic plaque and the vessel wall was calculated by subtracting the background temperature from the maximal temperature of the lesion[15–19]. Finally, after pre-dilatation a stent was implanted in the target lesion.

Table 1 Baseline characteristics

	Treated (n=35)	Non-treated (n=37)	*P* value
Age (years)	58 ± 9	61 ± 9	ns
Male sex	31 (89%)	34 (92%)	ns
Effort angina	10 (29%)	11 (30%)	ns
Unstable angina	15 (42%)	17 (46%)	ns
Acute myocardial infarction	10 (29%)	9 (24%)	ns
Aspirin use	27 (77%)	31 (83%)	ns
ACE inhibitor use	13 (37%)	15 (40%)	ns
Beta-blocker use	29 (83%)	31 (84%)	ns
Nitrate use	33 (94%)	35 (95%)	ns
Hypertension	20 (57%)	22 (59%)	ns
Diabetes mellitus	10 (28%)	13 (35%)	ns
Total cholesterol (mg . dl^{-1})	201 ± 29	245 ± 38	<0·001
Current smoking (>1 cig . day^{-1})	16 (46%)	14 (38%)	ns

Statistical analysis

Continuous variables are presented as mean ± one standard deviation, while qualitative variables are presented as absolute and relative frequencies. In order to evaluate the effect of statin treatment (main factor of interest) on ΔT (outcome) an exploratory analysis was initially applied based on non-parametric procedures. In particular, Friedmans's rank test, Spearman's correlation coefficient, Mann–Whitney and Kruskal–Wallis criteria were applied in order to evaluate associations between temperature differences (ΔT) and treatment group (statin or not), clinical syndrome, lipid profile, age, treated vessel, diabetes mellitus, smoking status, hypertension, family history of premature coronary heart disease, reference diameter, minimal lumen diameter and aspirin, ACE inhibitor, or beta-blockers intake.

The presented figures show median and interquartile range (box-plots) due to the skewed distribution of ΔT. In order to evaluate the effect of statins on ΔT we applied multiple regression analysis. The final model was developed through stepwise elimination procedures for the selection of variables, using 5% for the probability for entering and 10% for the probability of removing a cofactor from the model. Pearson's residuals were calculated in order to evaluate the model's goodness-of-fit. All reported *P*-values are exact, based on two-sided non-parametric tests and compared to a significant level of 5%.

STATA 6 software was used for the calculations (STATA Corp, Lakeway Drive, Texas, USA).

Results

There were no significant differences between the treated and the untreated study groups in terms of age, smoking habits, prevalence of diabetes mellitus, hypertension, the distribution of clinical syndrome, reference diameter, minimal lumen diameter and aspirin or ACE inhibitor intake. Tables 1 and 2 show the baseline clinical and angiographic characteristics of each group, respectively. The treated group received statins for 4·2 ± 2·1 months. The distribution of statin agents among the treated patients was 34% atorvastatin (the majority 10 mg), 34% pravastatin (20 mg), 23% simvastatin (10 mg), 4% fluvastatin (40 mg) and 5% cerivastatin (0·3 mg). Statins were administered for the treatment of hypercholesterolaemia.

Table 2 Angiographic characteristics

	Treated (n=35)	Non-treated (n=37)	*P* value
Target vessel			
LAD	13 (38%)	15 (41%)	ns
LCx	11 (31%)	7 (18%)	ns
RCA	11 (31%)	15 (41%)	ns
Location			
Proximal	11 (31%)	7 (19%)	ns
Middle	17 (49%)	22 (59%)	ns
Distal	7 (20%)	8 (22%)	ns
RD (mm)	2·91 ± 0·4	2·97 ± 0·3	ns
MLD (mm)	0·93 ± 0·2	0·87 ± 0·3	ns

LAD=left anterior descending coronary artery; LCx=left circumflex coronary artery; RCA=right coronary artery; RD=reference diameter; MLD=minimal lumen diameter

Procedural temperature measurements

The measurements obtained for determination of background temperature were constant in each patient of the total study group, varying by only 0·05 °C, with a standard deviation from 0 to 0·032. The background temperature and the temperature of the blood did not differ (P=0·500). IVUS was performed in 62% of the cases. In contrast, ΔT differed significantly between the subgroups based on the presenting clinical syndrome. In patients with effort angina, ΔT was 0·31 ± 0·18 °C, while in patients with unstable angina it was 0·36 ± 0·28 °C and in patients with acute myocardial infarction ΔT was

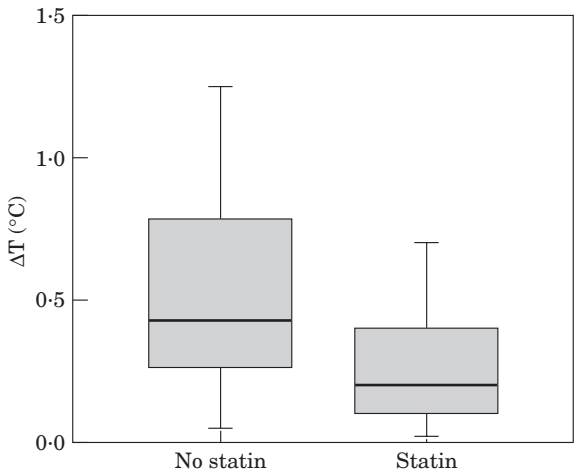

Figure 1 **Difference in atherosclerotic plaque temperature from background temperature (ΔT) between patients receiving statins and those without statins. The bottom of the box represents the first quartile; the top of the box represents the third quartile, and the line in the box represents the median value of ΔT.**

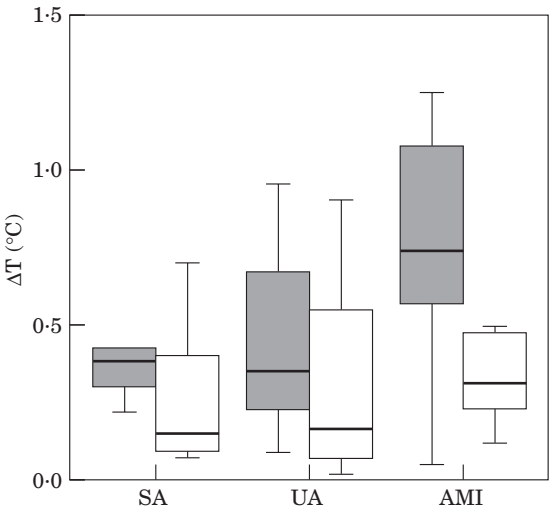

Figure 2 **The difference in atherosclerotic plaque temperature from background temperature (ΔT) was greater in patients without statin administration (□) than in patients receiving statins (□), in each type of clinical syndrome. The bottom of the box represents the first quartile; the top of the box represents the third quartile, and the line in the box represents the median value of ΔT. SA=stable angina, UA=unstable angina, AMI=acute myocardial infarction.**

Table 3 ΔT by treatment arm and type of syndrome

	Treated (n=37)	Non-treated (n=35)	*P*-value
EA (n=21)	0·24 ± 0·15 °C	0·41 ± 0·26 °C	<0·05
UA (n=32)	0·26 ± 0·26 °C	0·44 ± 0·28 °C	<0·05
AMI (n=19)	0·40 ± 0·28 °C	0·84 ± 0·52 °C	<0·05
P-value	0·23	<0·05	

ΔT=Difference in atherosclerotic plaque temperature from background temperature; EA=Effort angina; UA=unstable angina; AMI=acute myocardial infarction.

Table 4 Parameters coefficients of the regression model for the evaluation of ΔT (b-coefficient and standard error of the mean)

	Beta-coefficient	SEM	*P*-value
Statin	−0·21	0·09	0·01
Clinical syndrome	0·180	0·06	0·01
Age	−0·002	0·005	0·47
Hypertension	0·04	0·10	0·57
Diabetes mellitus	0·066	0·10	0·46
Total cholesterol (mg . dl^{-1})	0·03	0·11	0·83
Current smoking	−0·06	0·09	0·39
Family history of CHD	−0·03	0·09	0·95
Aspirin	−0·11	0·11	0·35
ACE inhibitors	0·08	0·12	0·510
Beta-blockers	0·08	0·12	0·610
RD	0·01	0·12	0·620
MLD	0·08	0·12	0·470

ΔT=Difference in atherosclerotic plaque temperature from background temperature; SE=standard error; ACS=acute coronary syndromes; EA=effort angina; CHD=coronary heart disease; ACE=angiotensin converting enzyme; RD=reference diameter; MLD=minimal lumen diameter.

0·68 ± 0·49 °C (*P*<0·001). Also, in the overall patient population, ΔT was lower in the statin-treated group compared to the untreated group (0·29 ± 0·33 vs 0·56 ± 0·41 °C, *P*<0·01) (Fig. 1). In Table 3 the mean ΔT values stratified by the type of syndrome, as well as by treatment arm, are presented. ΔT differs significantly in patients who received statins compared with patients who did not receive statins in all clinical syndromes. Figure 2 demonstrates the confounding effect of clinical syndrome on ΔT values. By multivariate analysis, statin treatment was found to be a significant predictor of ΔT variation after adjustment for the type of clinical syndrome and other potential co-factors (Table 4). ΔT did not correlate with the levels of cholesterol measured upon hospital admission.

Discussion

This study shows that statin treatment for a period exceeding 4 weeks is associated with reduced ΔT in patients with coronary artery disease. The administration of statins for a mean period of 4·2 ± 2·1 months before admission to hospital results in decreased ΔT in all clinical syndromes. Moreover, the effect of statins on ΔT may not be attributed to the lipid-lowering effect of statins, since there was no correlation between ΔT and levels of total cholesterol.

Statins, inflammation, and thermal heterogeneity

Thermal heterogeneity of atherosclerotic plaques is well correlated with inflammation, since the number of infiltrating macrophages is greater in plaques with increased temperature.[14] Accordingly, heat seems to be generated from inflamed atherosclerotic plaques containing an increased number of inflammatory cells that result in activation of plasma markers of inflammation such as C-reactive protein and serum amyloid A.[20]

The results of the present study support previous experimental and clinical studies indicating the favourable effect of statins on inflammatory markers, since heat generation was reduced in patients receiving statins. Experimental studies have shown that cholesterol lowering was accompanied by a reduction of inflammatory cells within the atherosclerotic plaque[25–26]. In a rabbit atherosclerosis model, atorvastatin decreased arterial macrophage infiltration and monocyte chemoattractant protein-1 in the neointima and media[27]. In the clinical setting, Strandberg *et al*. demonstrated that simvastatin or atorvastatin lowered C-reactive protein in hyperlipidaemic coronary patients[21]. Indeed, with respect to the clinical benefits of statins on C-reactive protein, the association between C-reactive protein and subsequent risk of recurrent coronary events was attenuated among patients assigned to pravastatin in the Cholesterol and Recurrent Events trial[22]. These effects were present even though patients with and without elevated levels of C-reactive protein had virtually identical baseline lipid levels. Further, pravastatin, atorvastatin, and simvastatin result in reduction of inflammatory markers to a similar extent in a period of 6 weeks, which is not related to the magnitude of lipid alterations observed[28]. In accordance with the findings of Jialal *et al*., the decreased temperature differences observed in this study were independent of the specific agents used.

Clinical implications

The current data demonstrate that ΔT is reduced in patients receiving statins for a period of $4{\cdot}2 \pm 2{\cdot}1$ months. This period seems to be adequate for the reduction of other inflammatory markers[29]. In addition to the mechanistic implications of these data, the fact that inflammatory markers decline in a brief period may be important for the timing of the initiation of statin therapy in several clinical settings. In addition, this observation supports the hypothesis that plaque stabilization may be a critical mechanism of effect for these agents.

The decreased ΔT found in patients receiving statins may have significant applications in the selection of patients with coronary artery disease for aggressive treatment with statins. Previous studies have shown that although statin agents are associated with reduced mortality, this clinical benefit of statin treatment was observed primarily in those patients with elevated markers of inflammation[22–23]. Although in this study the exact mechanism by which ΔT was reduced in treated patients was not investigated, future studies are needed to investigate whether this is related to plasma lipid level reduction or to the antiinflammatory effect of statins.

Study limitations

The present study was retrospective and with a small number of patients, and thus lacks the power of prospective assessment. A technical consideration is the detection of a normal vessel wall for the determination of background temperature. We used IVUS in the majority of the cases (62%) and in the rest of the cases the detection of a normal vessel wall was based on angiography, a method known to be associated with several shortcomings[30]. However, we found no differences between blood and normal wall, and also the measurements obtained for determination of background temperature were constant in each patient (SD=0 to 0·032). These findings imply that the area used for background temperature was free of disease according to previous experience[15–16].

The treated group was not homogeneous since several different statin agents were administered. However, other investigators suggest that the antiinflammatory effect of statins is observed in the majority of statins[28]. In addition, the duration of statin intake and the dose–response effect of statins on ΔT could not be assessed. Finally, several confounding factors for temperature measurements were considered, however, it was not possible to eliminate the effect of several unmeasured confounders that may exist.

Conclusions

This study demonstrates that statin treatment is associated with a reduced temperature difference between the coronary atherosclerotic plaque and the vessel wall. The mechanism by which statin treatment is associated with reduced thermal heterogeneity is still not elucidated. However, the results of this study provide evidence in support of the antiinflammatory effects of statins in humans.

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