Thermal Heterogeneity in Stable Human Coronary Atherosclerotic Plaques Is Underestimated In Vivo: The “Cooling Effect” of Blood Flow

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OBJECTIVES
This study investigated whether temperature measurements are influenced by blood flow. Previous ex vivo studies showed marked thermal heterogeneity in atheromatous plaques. In stable lesions, however, trivial in vivo temperature variations are recorded, perhaps due to the “cooling effect” of blood flow.

BACKGROUND
Eighteen patients with effort angina were studied. Coronary flow velocity was continuously recorded; over another guidewire, temperature measurements were performed at the proximal vessel wall and at the lesion before, during, and after complete interruption of blood flow by inflation of a balloon. The ΔTp was assigned as the difference between the proximal vessel wall temperature and the maximal temperature during and after balloon inflation. The ΔTl was assigned as the difference between the atherosclerotic plaque and the proximal vessel wall.

METHODS
The procedure was not complicated. During and after complete interruption of flow, ΔTp was 0.012 ± 0.01°C and −0.006 ± −0.01°C (p < 0.001), respectively. The ΔTl was 0.08 ± 0.04°C at baseline and went to 0.18 ± 0.05°C (60.5 ± 14.1% increase) during and 0.08 ± 0.04°C after flow interruption (p < 0.001). The ΔTl was greater than ΔTp during and after impairment of flow (p < 0.001). A correlation between the baseline average peak velocity and ΔTl during flow interruption was found (R = 0.57, p = 0.01). In seven patients thermal heterogeneity was not detected at baseline, and during balloon inflation ΔTl increased by 76.0 ± 8.4%.

RESULTS
CONCLUSIONS. Thermal heterogeneity is underestimated in atherosclerotic plaques in patients with effort angina. Potential in vivo underestimation of heat production locally in human atherosclerotic disease and myocardial infarction less than one month associated with an acute-phase response were not enrolled in the study. Moreover, patients with intercurrent inflammatory or neoplastic condition likely to be associated with an acute-phase response were not enrolled in the study. Exclusion criteria also included multivessel disease and myocardial infarction less than one month before intervention.

Both ex vivo and in vivo studies have demonstrated thermal heterogeneity in human atherosclerotic plaques (1,2). Thermal heterogeneity is increased in unstable atherosclerotic plaques compared to stable plaques (1). Patients with effort angina have decreased thermal heterogeneity compared to patients with acute coronary syndromes. Recent studies have also shown that, by dietary or pharmacologic intervention, thermal heterogeneity may be decreased (3,4). In an experimental model, reduction of thermal heterogeneity of aortic atherosclerotic plaques was accomplished after cholesterol lowering (3). In humans, administration of 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors (statins) was accompanied by decreased thermal heterogeneity in coronary atherosclerotic plaques (4).

The identification of lesions with thermal heterogeneity is also important for the risk stratification after percutaneous coronary intervention. Patients with treated lesions with increased temperature have unfavorable prognosis compared to patients without increased thermal heterogeneity in culprit lesions (5).

In several significant lesions, however, temperature variations cannot be detected or trivial changes are recorded. Especially in patients with effort angina, in only 20% of them was thermal heterogeneity found (1). However, the ex vivo temperature variations were greater than the reported in vivo thermal heterogeneity (2).

A possible mechanism for the in vivo underestimation of thermal heterogeneity within human atherosclerotic plaques is the effect of blood flow. The “cooling effect” of blood flow on temperature measurements has not been investigated. The aim of this study was to investigate whether temperature measurements are influenced by blood flow.

METHODS

Study population. Inclusion criteria were patients suffering from effort angina with single lesion <20 mm in length in a major native coronary artery with proximal reference vessel diameter ≥2.5 mm.

Patients under medication with corticosteroids or non-steroidal anti-inflammatory drugs except for aspirin, were excluded from the study. Moreover, patients with intercurrent inflammatory or neoplastic condition likely to be associated with an acute-phase response were not enrolled in the study. Exclusion criteria also included multivessel disease and myocardial infarction less than one month before intervention.
According to these criteria the study population consisted of 18 consecutive patients. Baseline demographic and procedural variables were recorded and entered prospectively in a prespecified database. The study protocol was approved by the institutional ethical committee, and each patient provided written informed consent.

**Thermography catheter.** The design and construction characteristics of the coronary thermography catheter (Epiphany, Medispes SW A.G., Zug, Switzerland) have been previously described in detail (1,4–5). In brief, the technical characteristic of the polyamide thermistor include 1) temperature accuracy of 0.05°C, 2) time constant of 300 ms, 3) spatial resolution of 0.5 mm, and 4) linear correlation of resistance versus temperature over the range of 33°C to 43°C. Opposite the thermistor is a hydrofoil specifically designed to ensure contact of the thermistor on the vessel wall.

**Procedure.** The culprit lesion of interest was outlined in ≥2 well-opacified views with biplane angiography. These projections were obtained before and after the procedure. The study protocol is summarized in Figure 1.

Through a 7F guiding catheter, a conventional guidewire and a 0.014-in. Doppler-tipped guidewire (Flowire, Cardiometrics, Mountain View, California) were advanced distal to the target lesion. The second guidewire was positioned approximately 3 cm distal to the lesion in the target vessel and positioned until an optimal and stable Doppler signal, not in the proximity of a side branch, was obtained. The instantaneous coronary flow velocity and the electrocardiogram were continuously displayed throughout the study and recorded on videotape. Average peak velocity (cm/s) was derived automatically by the integrated signal-analyzing computer (6–8).

Five minutes after any contrast injection, the 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 vessel wall—evaluated by intravascular ultrasound (Endosonics Europe B.V., Ulestradten, The Netherlands)—and the most frequent temperature was designated the proximal vessel wall temperature. Afterwards, temperature recordings at the atherosclerotic lesion were performed.

A balloon-catheter (Cronus, Medispes SW A.G., Zug, Switzerland) was then introduced over the Doppler-tipped guidewire to a site just proximal to the lesion; temperature of the atherosclerotic plaque was continuously recorded. To avoid injury, the maximum pressure that was scheduled for interruption of flow was 3 atm. Therefore, the selection of the diameter of the balloon was 0.5 mm larger than the diameter of the proximal reference vessel. The balloon was then progressively inflated until flow was completely interrupted. The balloon was inflated with a mixture of contrast medium and normal saline at 37°C (Fig. 2). After balloon deflation, the balloon catheter was withdrawn and temperature was continuously recorded at the lesion. The balloon catheter was then advanced at the proximal nondiseased segment in which baseline temperature measurements were performed, and the thermography catheter was withdrawn proximally. The thermistor of the thermography catheter was placed just distal to the balloon. The balloon was progressively inflated until the flow was completely interrupted. After balloon deflation, the balloon catheter and the thermography catheter were withdrawn and all patients underwent stent (Zeus, Medispes SW A.G., Zug, Switzerland) implantation using standard technique. Coronary flow velocity was also recorded during and after stent placement.

In all patients, creatine kinase (CK) and creatine kinase–MB fraction (CK-MB) were measured at 6 and 12 h after the procedure. The Q-wave myocardial infarction (MI) was documented by the presence of new Q waves of at least 0.04 in duration and a CK level, with a positive CK-MB fraction, at least twice the upper limit of normal. Non-Q-wave MI was defined as an elevation of CK greater than twice the normal value, with a positive CK-MB fraction, without development of new Q-wave.

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**Abbreviations and Acronyms**

- CK = creatine kinase
- CK-MB = creatine kinase-MB fraction
- MI = myocardial infarction
- ΔTI = difference between the atherosclerotic plaque and the proximal vessel wall
- ΔTP = difference between the proximal vessel wall temperature and the maximal temperature during complete flow interruption and after balloon deflation

**Figure 1.** A summary of the sites of temperature measurements for the computation of ΔTI (difference between the atherosclerotic plaque and the proximal vessel wall) and ΔTP (difference between the proximal vessel wall temperature and the maximal temperature during complete flow interruption and after balloon deflation). After recording the temperature at the proximal vessel wall (PVW) at baseline, three measurements were obtained at the lesion: 1) at baseline, 2) during coronary flow interruption, and 3) after balloon deflation. Thus, ΔTI was obtained at these three phases of the study. Thereafter, temperature was recorded at the PVW: 1) during coronary blood flow interruption, and 2) after balloon deflation. The ΔTP was obtained at these two phases, respectively.
All patients were discharged from the hospital with ticlopidine or clopidogrel for one month, and aspirin, statins, and standard medical therapy indefinitely.

**REPRODUCIBILITY.** Duplicate measurements were obtained in each coronary artery. The data of the first series of measurements were used for data analysis; the data of the second measurement were solely used to assess the reproducibility.

**Definitions.**

**DIFFERENCE OF TEMPERATURE AT THE LESION (ΔTl).** Difference 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 at baseline, during complete occlusion of the flow, and balloon deflation.

**DIFFERENCE OF TEMPERATURE AT THE PROXIMAL SEGMENT (ΔTp).** Difference between the proximal vessel wall temperature and the maximal temperature during balloon occlusion and after balloon deflation was calculated by subtracting the proximal vessel wall temperature from the maximal temperature during complete occlusion of the flow and after balloon deflation, respectively.

**Quantitative angiographic and coronary volumetric flow measurements.** Quantitative coronary angiographic measurements were performed on-line. A computer-assisted analysis system was used for quantitative coronary angiography (DCI-S, Automated Coronary Analysis, Philips, The Netherlands). Automated edge-detection of the minimal lumen diameter and reference diameter were measured by use of the guiding-catheter filled with contrast as a scaling factor. The minimal lumen diameter and the percent diameter stenosis were measured in a standard manner. Quantitative angiographic measurements of luminal diameter were used to calculate coronary cross-sectional area. Coronary volumetric flow was then calculated as the product of average peak velocity × 0.5 (correction factor assuming parabolic flow profile) × the cross-sectional area of the target vessel 5 to 10 mm distal to the Doppler-guidewire tip location.

Lesions were characterized according to the modified American College of Cardiology American Heart Association classification (9).

**Statistical analysis.** Continuous variables are presented as mean ± 1 standard deviation and qualitative variables as absolute and relative frequencies. Comparison of ΔTl at baseline, during balloon occlusion, and after balloon deflation was performed by analysis of variance for repeated measurements. Paired t test was used for comparison of ΔTp and ΔTl during flow interruption and after balloon deflation. Correlation between baseline average peak velocity with ΔTl during balloon inflation was performed by Spearman’s correlation coefficient. All p values are two-sided and compared to a significant level of 5%. STATA 6 software was used (STATA, College Station, Texas).

**RESULTS**

Baseline clinical and angiographic characteristics are demonstrated in Tables 1 and 2, respectively. The majority of the patients were receiving statins 5.3 ± 7.8 months before the intervention. The procedural characteristics are shown in Table 2. Flow was obstructed by inflation of the balloon to 2.5 ± 0.5 atm. The duration of the balloon inflation was...
Table 1. Baseline Characteristics

<table>
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<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Number</td>
<td>18</td>
</tr>
<tr>
<td>Male patients</td>
<td>17 (94%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>62 ± 7</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>214 ± 33</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>7 (39%)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>10 (56%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>18 (100%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>12 (67%)</td>
</tr>
<tr>
<td>Statin</td>
<td>15 (83%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>12 (67%)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>52 ± 10</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>1 (6%)</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
ACE = angiotensin-converting enzyme; CAD = coronary artery disease; EF = ejection fraction; PTCA = percutaneous transluminal coronary angioplasty.

10 ± 2 s. In all cases the procedure was not complicated neither CK nor CK-MB was elevated after the procedure.

Coronary blood flow measurements. The mean average peak velocity at baseline and after balloon deflation was 13.06 ± 1.80 cm/s and 23.33 ± 4.87 cm/s, respectively. After stent implantation, coronary flow velocity was 41.89 ± 3.32 cm/s. Coronary volumetric flow was increased from 29.23 ± 5.32 ml/min at baseline to 65.62 ± 15.59 ml/min after stent implantation.

Temperature measurements. Measurements obtained for determination of proximal vessel wall temperature were constant in each patient of the total study group, varying by only 0.02°C, with a standard deviation from 0 to 0.03. The temperature of the proximal vessel wall and the temperature of the blood did not differ (p = 0.54).

The ΔTp was 0.012 ± 0.01°C during complete occlusion of the flow, and after deflation of the balloon it was −0.006 ± −0.01°C (p < 0.001). The ΔTI was 0.08 ± 0.04°C at baseline, and it was increased by 60.5 ± 14.1% during complete occlusion as it was 0.18 ± 0.05°C and 0.08 ± 0.04°C after balloon deflation (p < 0.001) (Fig. 3).

The ΔTI was greater than ΔTp during impairment of flow (p < 0.001) and after balloon deflation (p < 0.001). At baseline and after balloon deflation, ΔTI was not different (p = 0.98). A correlation between the difference of average peak velocity from baseline values with ΔTI during flow interruption was found (R = 0.57, p = 0.01) (Fig. 4).

In seven patients, thermal heterogeneity was not detected at baseline (ΔTI was <0.05°C). However, during balloon inflation ΔTI increased by 76.0 ± 8.4% to 0.11 ± 0.02°C, and immediately after restoration of flow ΔTI was 0.03 ± 0.005°C (Fig. 5).

Reproducibility. The second measurements for ΔTI varied by only 0.02°C (range 0 to 0.03) at baseline, during balloon inflation and after balloon deflation. The variation for ΔTp was 0.01°C (range 0 to 0.02).

DISCUSSION

The major findings of this study are: 1) thermal heterogeneity is underestimated in vivo in stable athromotic plaques, and 2) blood flow influences the in vivo temperature measurements in athromotic plaques.

Thermal heterogeneity has been detected ex vivo and in vivo in human atherosclerotic plaques (1,2,10). In the in vivo studies, however, detected temperature variations were less compared to ex vivo studies (1,2). Furthermore, in several significant lesions temperature variations could not be detected or trivial changes were recorded (1). Especially in patients with effort angina, only in a minority (20%) of patients was thermal heterogeneity detected. A significant factor leading to these diverse results may be the “cooling effect” of blood flow. Blood flow may increase the heat transfer from the atherosclerotic plaque; consequently, the local temperature on the surface of the lesion may be underestimated.

By complete occlusion of the blood flow, the temperature difference between the proximal vessel wall, which by intracoronary ultrasound was free of disease, and the atherosclerotic plaque increased by 60.5%. This increase was greater (76.0%) in patients with lesions in which, at baseline measurements, thermal heterogeneity was not detected. The absolute change in coronary flow velocity was inversely related to the temperature difference between the atherosclerotic plaque and the reference site.

Technical considerations. We used this protocol to investigate whether thermal heterogeneity exists in all plaques and to determine the effect of blood flow on temperature measurements. Advancement of the balloon catheter just...
proximal to the thermistor, which was located at the atherosclerotic plaque, provided, firstly, the ability to completely occlude the vessel by the inflation of the appropriately selected balloon in terms of size, and, secondly, to ensure contact of the thermistor with the atherosclerotic plaque during flow interruption. As the balloon was inflated just proximal to the site of the lesion, the thermistor was in contact with the plaque. This is proved by the increase of temperature in all lesions during the balloon inflation and by the drop of temperature to baseline values after balloon deflation. These results were reproducible in the second series of measurements.

In addition, the effect of flow on these measurements is clearly demonstrated by the continuous recording of the flow distal to the lesion, the inverse correlation of blood flow velocity with the temperature difference at the lesion, and the unchanged temperature measurements during balloon inflation in the proximal nondiseased reference segment.

**Clinical implications.** The results of this study demonstrate that thermal heterogeneity exists even in stable plaques and the “cooling effect” of blood flow may lead to underestimation of in vivo temperature measurements in the atherosclerotic plaques. This finding may be important as the identification of plaques with thermal heterogeneity provides information regarding the local process of inflammation (2,3) and has prognostic value after percutaneous

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**Figure 3.** Difference between the proximal vessel wall temperature and the maximal temperature during complete flow interruption and after balloon deflation ($\Delta T_p$) (left) and difference of temperature ($\Delta T$) between the atherosclerotic plaque and the proximal vessel wall ($\Delta T_l$) at baseline, during complete occlusion of flow, and after balloon deflation (right). 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 $\Delta T_p$ or $\Delta T_l$. The broken vertical line differentiates the measurement for $\Delta T_p$ and $\Delta T_l$.

**Figure 4.** Graph showing the correlation between the difference of average peak velocity (AVP) from baseline values with $\Delta T_l$ (difference of temperature between the atherosclerotic plaque and the proximal vessel wall) during balloon inflation.
coronary interventions (5). Because dietary (3) or pharmacologic (4) interventions may reduce atherosclerotic plaque temperature, accurate temperature measurements may be used for the selection of patients for aggressive treatment for stabilization of plaques potentially prone to rupture and producing acute ischemic events. Furthermore, blood flow effect needs to be considered in the evolving technology of catheter-based or noninvasive techniques for temperature measurements in human atherosclerotic plaques.

Regarding the safety of the technique, although two guidewires were used we did not observe any complication during the procedure. The inflation of the balloon proximal to the lesion was performed with low pressure and for a short period of time. Cardiac enzymes were within the normal limits after the procedure.

Study limitations. The number of patients included in the study was rather small. The group of patients, however, was homogeneous regarding the clinical syndrome, the medication, and the angiographic characteristics. Although the role of coronary blood flow is revealed in this study we cannot exclude other potential unknown confounders for the observed increase of atherosclerotic plaque temperature during obstruction of blood flow.

The effect of blood flow was demonstrated in symptomatic patients with angiographically severe stenoses. Intermediate or low-grade stenoses in asymptomatic patients could not be studied with this technique, because incomplete opposition of the thermistor to these atherosclerotic lesions due to turbulent flow may lead to underestimation of the baseline thermal heterogeneity of the plaque. In this study, however, only lesions producing significant stenoses were included. The identification of thermal heterogeneity in nonsignificant stenoses may require a different technology.

Conclusions. Thermal heterogeneity exists in all atherosclerotic plaques even in patients with effort angina with significant stenoses. Potential in vivo underestimation of heat production locally in human atherosclerotic plaques with currently available technology is due to the “cooling effect” of coronary blood flow.

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REFERENCES