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Intracoronary Thermography for Detection of High-Risk Vulnerable Plaques

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Up to two-thirds of acute myocardial infarctions develop at sites of culprit lesions without a significant stenosis. New imaging techniques are needed to identify those lesions with an increased risk of developing an acute complication in the near future. Inflammation is a hallmark feature of these vulnerable/high-risk plaques. We have shown that inflamed atherosclerotic plaques are hot and their surface temperature correlates with an increased number of macrophages and decreased fibrous-cap thickness. Multiple animal and human experiments have shown that temperature heterogeneity correlates with arterial inflammation in vivo. Several coronary temperature mapping catheters are currently being developed and studied. These thermography methods can be used in the future to detect vulnerable plaques, potentially to determine patients' prognosis, and to study the plaque-stabilizing effects of different medications. (J Am Coll Cardiol 2006;47:C80–5) © 2006 by the American College of Cardiology Foundation

Atherosclerosis is an inflammatory disease (1). In the mid-1990s, our group (S.W.C. and J.T.W.) investigated whether heat, a 2,000-year-old clinical sign of inflammation, can be used to locate foci of inflammation in the arterial wall (2). These experiments were based on the hypothesis that if atherosclerotic lesions are inflamed by virtue of inflammatory cell infiltration, they will give off more heat than normal areas of the arterial system. The possible reasons for this increased heart production are summarized in Table 1.

High metabolic rate. Macrophages, T-cells, and mast cells are very active cells with a high metabolic rate and high rate of energy consumption (3,4). In fact, the turnover rate for the total adenosine triphosphate (ATP) content of the macrophage in culture is about half of that for a perfused, isolated, maximally working rat heart (3). Arterial foam cells consume three times more oxygen than isolated smooth-muscle cells (5).

Ineffective thermogenesis. Many areas of atherosclerotic plaques are known to be ischemic, and the lack of oxygen would lead to ineffective metabolism of nutrients and greater loss of energy in the form of heat instead of ATP production. More interestingly, macrophages in atherosclerotic plaques show increased expression of mitochondrial uncoupling protein (UCP)-2 and UCP-3 (6). Uncoupling proteins are homologues of thermogenin (UCP-1), and may contribute to heat production in plaques in the same way that thermogenin causes thermogenesis in brown fat tissue.

Increased neoangiogenesis. There is a high rate of neoangiogenesis in vulnerable plaques (7,8). Neovessel formation increases blood flow inside plaques, with resulting higher temperatures (although they may hypothetically "wash the heat away" from the plaque and work in the opposite direction).

Infections. Several infectious agents, such as *Chlamydia pneumoniae*, herpes viruses, and influenza, have been suggested to play a role in atherosclerosis (9–11). The possible local infection and subsequent inflammation may contribute to plaque heat production.

The final measured surface temperature over the arterial wall will depend on: 1) the metabolic activity of cellular components of plaques (especially more superficial cells), 2) heat diffusion to and from adjacent tissues, and 3) blood-tissue thermal diffusion (12).

THERMAL HETEROGENEITY OF ATHEROSCLEROTIC PLAQUES, EX VIVO STUDIES

In a series of proof-of-concept studies, we measured the intimal surface temperatures of carotid artery plaques obtained during endarterectomy (2). In a heat- and humidity-controlled environment, we measured the surface temperature of multiple sites on each plaque by using a needle thermistor. In the absence of blood flow, we found significant temperature variations ranging from 0.2°C to 2.2°C (Fig. 1). Temperature heterogeneity could also be confirmed using an infrared camera. Measured temperature was directly correlated with cell density ($r = 0.68$; $p = 0.0001$) and inversely correlated with the depth of the cell clusters ($r = -0.38$; $p = 0.0006$) (2). Interestingly, temperature showed a positive correlation with macrophage density ($r = 0.66$; $p = 0.0001$) and an inverse correlation with smooth-muscle-cell density ($r = -0.41$; $p = 0.0001$) (13). Temperature heterogeneity did not correlate with the presence of *C. pneumoniae,* nor with the gross color of the luminal surface of plaques (13).

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Abbreviations and Acronyms

AMI = acute myocardial infarction
ATP = adenosine triphosphate
CRP = C-reactive protein
EA = effort angina
IVUS = intravascular ultrasound
MMP = matrix metalloproteinase
ΔTmax = maximum temperature difference
UA = unstable angina
UCP = uncoupling protein

We also observed lower pH readings in vulnerable plaques in human carotid endarterectomy specimens, atherosclerotic rabbit aortas, and apoE-deficient mice aortas (14). In these samples, a lower pH was associated with a higher temperature ($r = 0.7$; $p < 0.0001$). Lipid-rich areas had a lower pH and a higher temperature, whereas calcified areas showed a higher pH and a lower temperature (14). Temperature and pH were significantly and inversely correlated ($r = 0.94$; $p < 0.001$) (Fig. 2).

TEMPERATURE MAPPING OVER ARTERIAL WALLS—ANIMAL STUDIES

Naghavi et al. (15) developed a contact-based "thermobasket" catheter for measuring the in vivo temperature over the arterial wall. This is a thermocouple-based basket catheter equipped with four small, flexible wires with built-in thermocouples and a thermal sensor in its central wire for simultaneous monitoring of the blood temperature. The device has a thermal resolution of 0.02°C with a sampling rate of 20 temperature readings per second. In animal studies, this catheter could detect temperature heterogeneity over the atherosclerotic plaques in the femoral arteries of inbred atherosclerotic dogs (Fig. 3) and the aortas of Watanabe rabbits (15,16).

Verheye et al. (17) developed an over-the-wire thermography catheter with four thermistors. They used it in 20 New Zealand rabbits randomized to either a normal diet or a cholesterol-rich diet for six months. They found marked temperature heterogeneity (up to 1°C) in the hypercholesterolemic rabbits at sites of thick plaques (assessed by intravascular ultrasound [IVUS]), where histology showed a high macrophage density. Temperature heterogeneity was absent at sites of plaques with a low macrophage density. Three months of a low-cholesterol diet led to a significant decrease in macrophage content in the absence of any changes in plaque thickness (17).

Table 1. Hypothetical Mechanisms of Heat Production in Plaque

Inflammation
Activated macrophages, T cells
Infections
Increased neovessel formation
Ineffective energy metabolism
Thermogenesis (uncoupling proteins)

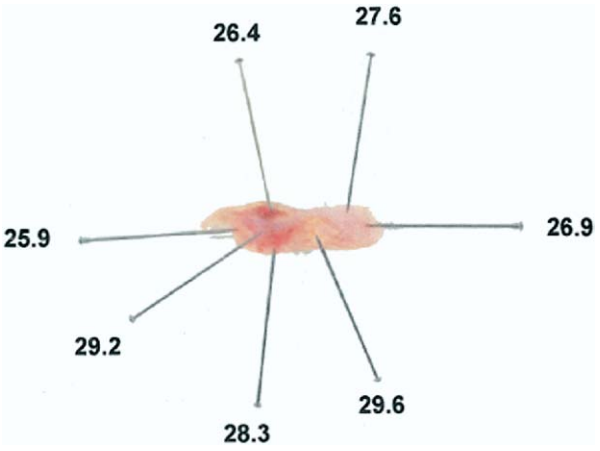

Figure 1. Endarterectomized carotid plaques show temperature heterogeneity. Reprinted, with permission, from Madjid et al. (16).

EFFECT OF BLOOD FLOW ON CORONARY TEMPERATURE MEASUREMENT

Coronary flow may exert a "cooling effect" on measured coronary temperature. Complete obstruction of blood flow may increase the degree of detected temperature heterogeneity by 60% to 76% (18). However, others have shown that normal physiological flow conditions reduce temperature heterogeneity only by 8% to 13% compared to surface temperature measured in the absence of flow (19).

Diamantopoulos et al. (20) studied Thermosense thermography catheters (Thermocore Medical Ltd., Guildford, United Kingdom) in pigs and found that flow velocities above an average peak velocity of 9 cm/s do not affect temperature measurements. At flow velocities around 4 cm/s, the wall temperature began to rise by 0.015 ± 0.005°C, and further decrease in flow velocity causes a logarithmic increase in local wall temperature to a maximum

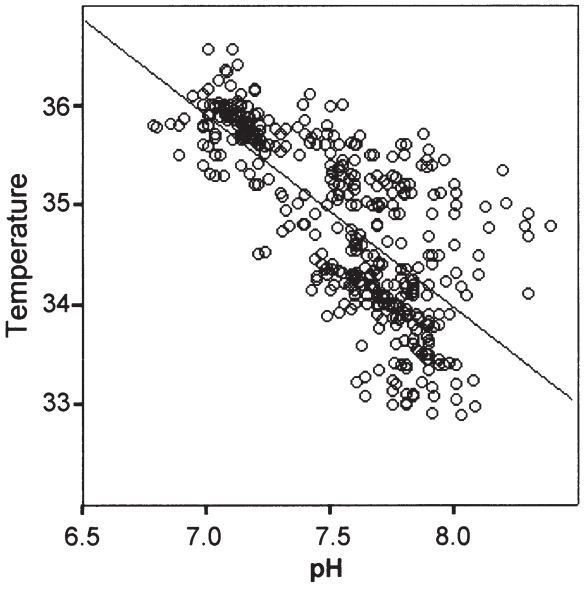

Figure 2. Inverse correlation of pH and temperature (°C) in human carotid artery plaques. Reprinted, with permission, from Madjid et al. (16).

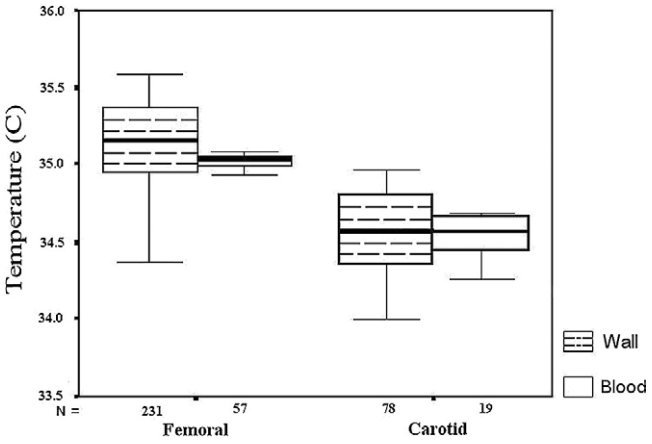

Figure 3. Studies with thermobasket catheter showed higher absolute temperature as well as temperature heterogeneity in femoral arteries of atherosclerotic dogs compared to their carotid arteries, which are free of disease. Adapted, with permission, from Madjid et al. (16).

of 0.188 ± 0.023°C, observed at total vessel occlusion. Importantly, in normal arteries, periodic oscillation in the flow velocity did not affect wall temperature. A mathematical simulation of a model of a coronary artery segment containing a heat source predicted that measured temperature is strongly affected by blood flow and also by cap thickness and source geometry (21).

On the basis of these studies, proximal occlusion of the artery by use of a balloon has been suggested to improve the temperature reading from the arterial wall and to overcome the problems arising from the cooling effects of blood flow.

INTRACORONARY THERMAL DETECTION—HUMAN STUDIES

Stefanadis et al. (22) in Greece conducted the first human intracoronary thermographic study in 1999. They used a rather large single-channel, thermistor-based catheter which almost blocked the arterial lumen, therefore decreasing the heat-dissipating effect of blood flow. In this study, temperature differences (ΔT) between atherosclerotic plaque and healthy vascular wall was 0.10 ± 0.11°C in patients with stable angina, 0.68 ± 0.34°C in those with unstable angina (UA), and 1.47 ± 0.69°C in patients with acute myocardial infarction (AMI). Plaque temperature heterogeneity was present in 20%, 40%, and 67% of the patients with stable angina, UA, and AMI, respectively, and did not correlate with the degree of stenosis. Temperature heterogeneity was absent in the control group.

In more recent studies, lower degrees of temperature difference have been reported by Webster et al. (23), Verheye et al. (24), Schmermund et al. (25), and Erbel et al. (personal correspondence, 2003). These differences may be caused in part by the discrepancies in the use of various medications (e.g., statins, aspirin) which may stabilize hot plaques, and more importantly, the effects of thermography catheters on blood flow. The larger thermistor used by Stefanadis et al. (18) can "wedge" the lesion and obstruct blood flow, whereas more recent studies have used catheters which do not obstruct coronary blood flow.

Schmermund et al. (25) used a non-occluding thermography catheter (Volcano Therapeutics, Orange County, California) in patients undergoing coronary intervention. This catheter system has a self-expanding basket with five nitinol arms at its tip, with one thermocouple on each arm and another one on the central wire, allowing for real-time, cross-sectional thermal mapping of the arterial wall. They studied 19 patients (ages 60 ± 11 years), of whom 11 had stable angina and 8 had UA. Focal high temperature was determined by comparing the temperature between arterial wall thermocouples versus central thermocouple. They recorded temperature differences ranging from 0.14°C to 0.36°C. Focal temperature heterogeneity was observed in four (50%) UA patients and in three (27%) patients with stable angina. This study showed a difference between the two groups; however, there was still a considerable overlap.

Wainstein et al. (26) used a different thermography catheter (ThermoCoil Guidewire, Imetrx, Mountain View, California). This guidewire has a temperature sensor in the distal tip and consists of a 0.014-inch wire with an angled tip rotating at 0.5 Hz at a pullback scanning rate of 0.5 mm/s, inscribing a helix on the lumen. They studied 13 patients: 2 with UA, 1 with non–ST-segment elevation MI, 1 with ST-segment elevation MI, and 9 with stable angina. Intracoronary temperature rises (0.1°C to 0.3°C) were detected in four subjects.

Dudek et al. (27) recently reported a study of 40 acute coronary syndrome patients (16 UA, 24 AMI, ages 54 ± 10 years) using a multisensor thermography basket catheter with five wall thermocouples and a central blood thermocouple (VCN). They measured ΔTmax (°C), defined as the maximum temperature difference between blood and any thermal couple. Mean ΔTmax was 0.09 ± 0.03°C. ΔTmax (°C) was 0 to 0.05 in 4, 0.06 to 0.09 in 19, and 0.1 to 0.28 in 16 patients. Average ΔTmax at the culprit segment (measured in 23 patients) was 0.092 ± 0.03°C (range 0.04°C to 0.18°C), which was significantly higher than ΔTmax recorded at a non-culprit (0.06 ± 0.01°C, range 0.03°C to 0.28°C, in 15 patients) ($p = 0.0006$). ΔTmax did not correlate with systemic high-sensitivity C-reactive protein level or previous statin use but had inverse correlation with blood flow during thermal mapping. Presence of blood flow led to a significant decrease in the recorded difference between culprit and non-culprit segments ΔTmax (27).

EFFECT OF TEMPERATURE CUT POINT ON NUMBER OF HOT PLAQUES

Webster et al. (23) and Erbel et al. (personal correspondence, 2003) from New Zealand and Europe have collectively studied 6 patients with UA and 14 patients with stable angina. A cutoff temperature of ≥0.1°C yielded 10 patients with no temperature heterogeneity, 4 patients with a single hot spot, 3 patients with 2 hot spots, and 3 patients with 3

hot spots. However, an alternative cutoff of ≥0.2°C results in only 2 of 17 patients with a hot spot, and 1 patient with 2 such lesions. Changes in temperature cut points clearly and expectedly affect the number of detected hot plaques. Prospective cohort studies are needed to determine the optimum temperature cutoff level which can identify lesions that will benefit most from various interventions.

INTRACORONARY TEMPERATURE HETEROGENEITY AND SYSTEMIC INFLAMMATION

Stefanadis et al. (28) studied serum inflammatory biomarkers in 60 patients with stable angina, UA, and AMI, compared to 20 gender- and age-matched control subjects without coronary artery disease. In their study, there was a strong correlation between C-reactive protein (CRP) and serum amyloid A levels, with detected differences in temperature ($r = 0.796$, $p = 0.01$ and $r = 0.848$, $p = 0.01$, respectively). Wainstein et al. (26) found an apparently higher mean CRP level in patients with higher temperature heterogeneity compared to those without elevated temperature (14.0 vs. 6.2 mg/l, p = not reported) .

In contrast, in the studies by Webster et al. (23), and Erbel et al. (personal correspondence, 2003), most patients had normal serum CRP levels, and the number of hot plaques did not correlate with the CRP level (and degree of luminal stenosis). These discrepancies may be in part due to a higher use of statins and anti-inflammatory medications in the studies by Webster et al. (23) and Erbel et al. (personal correspondence, 2003), smaller sample sizes, and the nonrandomized nature of all observations.

Statin drugs have well-recognized anti-inflammatory effects and can reduce the number of macrophages while increasing the collagen content in atherosclerotic plaques, hence stabilizing the plaque (29,30). Stefanadis et al. (31) randomized 72 patients to a statin or placebo to investigate a possible stabilizing effect of statin on hot plaques. They found that statins significantly decrease the temperature difference in patients with stable angina, UA, and AMI (ΔT: 0.29 ± 0.33°C vs. 0.56 ± 0.41°C). This effect of temperature was independent of the serum cholesterol level at hospital admission and patients' presenting clinical syndrome.

TEMPERATURE HETEROGENEITY AND MARKERS OF PLAQUE VULNERABILITY

Temperature heterogeneity is associated with vascular remodeling (which is by itself associated with local inflammation in plaque) (32,33). Using IVUS in patients with acute coronary syndromes, Toutouzas et al. (34) have shown a strong and positive correlation between the coronary remodeling index (defined as the ratio of the external elastic membrane area at the lesion, to that at the proximal site) and the ΔT between the atherosclerotic plaque and healthy vascular wall. They have also reported a correlation between the serum matrix metalloproteinase (MMP)-9 concentration and ΔTs. Matrix metalloproteinases play important roles in vascular remodeling (35); however, the strength of the relationship between serum levels of MMPs and focal activity of such enzymes at the plaque level remains to be determined. Toutouzas et al. (36) used samples obtained through direct coronary atherectomy in eight patients and found a significant increase in MMP-1, -3, and -9 (determined by immunohistochemistry studies) in samples which showed high temperature differences.

TEMPERATURE HETEROGENEITY AND CLINICAL PROGNOSIS

Stefanadis et al. (37) investigated the midterm prognostic effect of human coronary atherosclerotic plaque temperature. They studied the temperature difference (ΔT) between the atherosclerotic plaque and the healthy vessel wall in 86 patients undergoing a successful percutaneous intervention. The patients had either effort angina (EA)

Table 2. Summary of Published Human Thermography Studies

Author(s)	Main Finding	Catheter
Stefanadis et al. (22)	Presence of T heterogeneity	Single-channel, thermistor-based
Stefanadis et al. (28)	Relation with CRP and same as above	Same as above
Stefanadis et al. (31)	Effect of statins	Same as above
Stefanadis et al. (37)	Effect on prognosis	Same as above
Toutouzas et al. (34)	Relation with remodeling and MMP-9 levels	Same as above
Schmermund et al. (25)	Presence of T heterogeneity	Volcano catheter: Self-expanding basket with five nitinol arms, one on each arm and one on the central wire
Wainstein et al. (26)	Presence of T heterogeneity relation with CRP	ThermoCoil guidewire: one temperature sensor on distal tip, a 0.014-inch wire with a rotating angled tip
Dudek et al. (27)	Presence of T heterogeneity Effect of blood flow	Volcano catheter
Webster et al. (23)	Presence of T heterogeneity No relation with CRP	Volcano catheter

CRP = C-reactive protein; MMP = matrix metalloproteinases.

(34.5%), UA (34.5%), or AMI (30%). The ΔT increased progressively from EA to AMI. Over a median clinical follow-up of 17.8 ± 7.1 months, the ΔT was a strong predictor of adverse cardiac events (odds ratio 2.14, p = 0.043). The threshold of the ΔT value, above which the risk for an adverse cardiac event was significantly increased, was 0.5°C.

CLINICAL IMPLICATIONS AND FUTURE RESEARCH

Thermography is a novel method for "functional imaging" of atherosclerotic plaques with a potential for detection of vulnerable plaques and identifying vulnerable patients. Currently, several thermography catheters are being studied in clinical trials in the U.S., Europe, and Oceania (Table 2) (38). These clinical trials need to determine the safety, reproducibility, and benefits of this imaging method. Major questions remain to be answered: What is the best cutoff value to define a hot plaque? What would be the sensitivity and specificity of such cutoff values in different clinical settings? Is it best to find focal increases in temperature or to define the general temperature burden in coronary segments? Is proximal occlusion necessary for thermography studies? Once a hot plaque or artery is identified, what would be the best clinical approach to manage it (39)?

Obviously, a number of clinical trials with different designs are needed to answer these questions. Vulnerable plaques have multiple characteristics, and a combination of thermography with anatomical imaging methods such as IVUS, elastography, or optical coherence tomography may be the best approach to identify them (16).

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