The percutaneous assessment of regional and acute coronary hot unstable plaques by thermographic evaluation (PARACHUTE) study: a prospective reproducibility and prognostic clinical study using thermography to predict future ischemic cardiac events

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The percutaneous assessment of regional and acute coronary hot unstable plaques by thermographic evaluation (PARACHUTE) study: a prospective reproducibility and prognostic clinical study using thermography to predict future ischemic cardiac events

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Intravascular thermography is currently being considered as a valuable tool in assessing macrophage-rich plaques. Since it is unknown what the prognostic value is of non-obstructive atherosclerotic plaques showing temperature heterogeneity, we designed the PARACHUTE study, a prospective, reproducibility, and prognostic clinical study using thermography in patients presenting with an unstable coronary syndrome. The primary endpoint of the study is the predictive value of temperature heterogeneity towards the occurrence of ischemic coronary events and hospitalization for ischemia and/or angina. The secondary endpoints are the predictive value of high-risk plaques associated with the development of future cardiac events, assessment of safety of the procedure, assessment of temperature reproducibility and heterogeneity in coronary arteries, as defined by the total thermal burden towards the occurrence of any cardiac event. Based on an event rate of death and myocardial infarction at 1 year of 10%, a sample size of 260 patients with presumed coronary artery disease, and positive troponin level who are scheduled to undergo an intervention will be included. All three main epicardial vessels will undergo angiography and thermography at baseline after revascularization of the flow-limiting vessel. At 12 months, angiography of all vessels and thermography of the vessel with the highest thermographic burden will be performed. Independent core laboratories will assess outcomes and a clinical endpoint committee will assess clinical events. (Int J Cardiovasc Intervent 2004; 2:69–75)

Introduction

Cardiovascular disease remains a considerable medical and socio-economic health problem since in the United States alone, each year over half a million people die of heart attacks or the consequences thereof.[1] Autopsy studies have shown that 68% of all myocardial infarctions are associated with lesions of less than 50% severity.[2–5] This means that small, non-obstructive and haemodynamically insignificant atherosclerotic plaques appear to be responsible for sudden death due to acute vessel closure and subsequent myocardial infarction. Today, interventional cardiologists do not tackle these potentially high-risk plaques for several reasons. First, there is no technique available today to identify the high-risk plaque. Second, it is unknown which of those plaques are harmful (leading to rupture) as not all plaques show an equally high risk of rupture. Furthermore, current standard technology such as coronary angiography is not able to predict the likelihood of rupture of such plaques, as it is also unable to visualize the plaques with reasonable specificity. Intravascular ultrasound (IVUS) as a means to interrogate the plaque may offer an attractive alternative, but until now, has not been able to predict coronary events. Since early detection is crucial, it is important that other techniques are

being developed to detect the high-risk plaque. Both non-invasive and invasive techniques have been introduced recently[6]. For the non-invasive detection, multi-slice computer tomography and magnetic resonance tomography are currently the front-runners. They offer the advantage of being non-invasive but have the disadvantages of low resolution, cardiac motion artifacts, and inability of analyzing distal segments of coronary arteries as well as being expensive. Invasive techniques may be disadvantageous because of their invasive approach, but on the other hand, these are capable of alleviating the problems seen by non-invasive techniques. Among the potential candidates for invasive techniques, there is thermography, optical coherence tomography, near-infrared spectroscopy, elastography—palpography and high-resolution intravascular ultrasound[7–11].

Several groups, including ours have reported on the possibility of using intravascular thermography to detect temperature heterogeneity, both in experimental conditions as well as in humans[7–8,12,13]. The experiments, both in animals and in humans, have shown that temperature heterogeneity is associated with presence of macrophages and that is predominantly present in patients with acute myocardial infarction and unstable angina. Temperature heterogeneity has been associated with inflammation, an important feature of the high-risk plaque, and it has been linked to clinical syndromes. We have designed the Percutaneous Assessment of Regional Acute Coronary Hot Unstable plaques by Thermographic Evaluation (PARACHUTE) study to try to find an answer to the following questions. What is the prognostic value of non-obstructive plaques with temperature heterogeneity? Can thermography indeed predict ischemic events? How heterogeneous are acute ruptured plaques? Does inflammation, represented by temperature differences, play a role in the vulnerability of a plaque? The definition of a new concept (defined as thermal burden) is introduced and described in the Objectives.

The PARACHUTE clinical study and population

The PARACHUTE study is a multi-centre, prospective, observational cohort study designed to assess, the reproducibility, and prognostic value of intravascular thermography. The aim of this study is to assess the value of thermography using the ThermoSense™ catheter (Guildford, UK) in the prognosis of ischemic cardiac events (ICE) and its components (death, myocardial infarction [MI], and coronary artery bypass grafting and repeat percutaneous transluminal coronary angioplasty) as well as hospitalisation for ischemia and/or anginal symptoms. The study population consists of patients presenting with an acute coronary syndrome within the last two weeks or an acute MI having elevated troponin above the upper limit of normal or unstable angina

(Braunwald class I-III B and C). Inclusion and exclusion criteria are shown in Table 1.

Objectives

The primary objective of the study is the predictive value of temperature heterogeneity towards the occurrence of ICE and hospitalisation for ischemia and/or anginal symptoms. Secondary objectives are the predictive value of high-risk plaques associated with the development of future cardiac events, the assessment of safety of the thermography procedure during initial hospitalisation, the assessment of temperature reproducibility and heterogeneity in coronary arteries, the predictive value of a different set of thermographic parameters towards the occurrence of any cardiac event. These thermographic parameters (Figure 1) are vessel thermographic burden (VTB or total area under the curve of all temperature increases measured for a particular vessel); normalized vessel thermographic burden (nVTB, or total area under the curve of all temperature increases measured for a particular vessel, normalized for the lowest value found); total thermographic burden (TTB, or total area under the curve of all temperature increases measured); normalized total thermographic burden (nTTB, or total area under the curve of all temperature increases measured, normalized for the lowest value found), all the above measures, averaged per cm of vessel (aVTB, anVTB, aTTB, anTTB). All the above measures will be performed not only with the mean temperature curve (derived from all four thermistors) but also with all independent temperature curves (including the curve that shows the highest temperature readings).

Thermal burden is a new theoretical concept that is trying to reflect a global assessment of temperature heterogeneity within the whole coronary artery tree or at least the analyzed segment. By interrogating the analyzed segment, thermal burden is expected to provide information on the inflammatory processes within the artery, a feature coinciding with plaque/clinical instability. By analyzing all three vessels, when possible (see Design), patients with single-vessel disease may serve as controls.

Design

A total of 260 patients with acute MI and elevated troponin above the upper limit of normal fulfilling all inclusion/exclusion criteria, will be included.

An attempt should be made to investigate all three main epicardiac vessels with the thermography catheter at baseline after PCI of the flow limiting vessel(s). Off-line quantitative coronary angiography (QCA) will be assessed of all three vessels. After thermography, patients will be monitored closely until they leave the hospital. At one, six and 12 months, a clinical follow-up visit will be scheduled. At 12 months follow-up, angiography and thermography of the vessel showing the highest thermo-

No Vulnerable Plaque (VP) in other vessels should be stented:

General and clinical criteria
a. Patients of both sexes, more than 18 years old, with typical symptoms of acute myocardial infarction and positive troponin.
b. Patients eligible for a diagnostic angiogram and coronary revascularization in native coronary artery/arteries.
c. Willing and able to comply with the specified follow-up evaluation.
d. Written informed consent obtained.
e. The target vessel(s) must be suitable for investigation with the thermography catheter as assessed by on-line QCA. The target vessel(s) must be a major coronary artery or major branch.
f. The subject must be an acceptable candidate for CABG.

Exclusion criteria
General and clinical criteria
a. Braunwald class IA, IIA, IIIA (unstable angina caused by non-cardiac illness).
b. Known allergies to aspirin, clopidogrel bisulfate, ticlopidine, heparin, stainless steel, copper or a sensitivity to contrast media which cannot be adequately pre-medicated.
c. Previous participation in this study or participation in another study with any investigational drug or device within the past 30 days (study participation ends after completion of the final follow-up).
d. Life expectancy of less than one year or factors making clinical and/or angiographic follow-up difficult.
e. Previous or planned CABG.
f. Planned major surgery.
g. Impaired renal function (creatinine >2 mg/dl or ≥150 μmol/L).
h. The subject has a history of bleeding diathesis or coagulopathy.
i. The subject suffered a stroke within the past year.
j. Coronary intervention within the last six months.

Criteria related to angioplasty
a. Left main coronary disease with ≥50% stenosis.
b. Minimal luminal diameter <2 mm in the segments to be analyzed.
c. Angiographic evidence of thrombus that cannot be resolved by therapy, occupying ≥50% of the target vessel segment diameter.
d. Ejection fraction ≤30%.
e. Previous bifurcation stenting in the segment(s) to be analyzed.
f. The proximal vessel is moderately to severely tortuous (moderate: two bends > 75° or one bend > 90°) in the segment(s) to be analyzed.
g. History of coronary vasospasm.
h. Presence of overlapping stents in segment(s) to be analyzed.
i. Planned stenting of vulnerable non-obstructive plaques.
j. Presence of chronic total occlusion in side branch.

Table 1
Inclusion and exclusion criteriax.

graphic burden at baseline will be performed (Table 2). If more than one vessel has the same value for thermographic burden, one vessel will be selected at the discretion of the investigator.

In addition, there will be four small subgroups of patients to:

(a) Stratify the reproducibility of thermography (15 patients will have thermography performed twice in all three main cardiac vessels at baseline).
(b) Find an association between thermography and IVUS in 30 patients (measurements at baseline and 1-year follow-up).
(c) Perform thermography in all three vessels at 1-year follow-up (30 patients).
(d) Register the reference temperature in the ascending aorta (15 patients).

Independent core laboratories (Cardialysis, The Netherlands) will assess angiographic/ IVUS outcomes and a clinical endpoint committee will assess clinical events.

The pullback of the catheter has to start from the indicated locations, differing per vessel: from the bifurcation posterior descending artery with the distal right of the right coronary artery, from the bifurcation second diagonal branch with the left anterior descending artery and from the bifurcation postero-lateral branch with the distal circumflex artery. If there is an intermediate branch (>2.5 mm), then a 30 mm pullback will be performed.

Statistics

Overall event rates of death and MI at one year are expected to be about 10%.[14,15] In order to distinguish the prognostic value of thermography, as assessed by average thermographic burden, 224 eligible patients are required to distinguish an Odds Ratio of 1.8 (=16.7% risk at $\mu + \sigma$) with a power of 80% and a 1-sided type I error rate of 5%, testing the null-hypothesis that the covariate (some measure of thermographic burden or temperature) has no influence on the prediction of endpoint events ($\beta = 0$) against the one-sided alternative hypothesis ($\beta > 0$), using the Wald test in a logistic
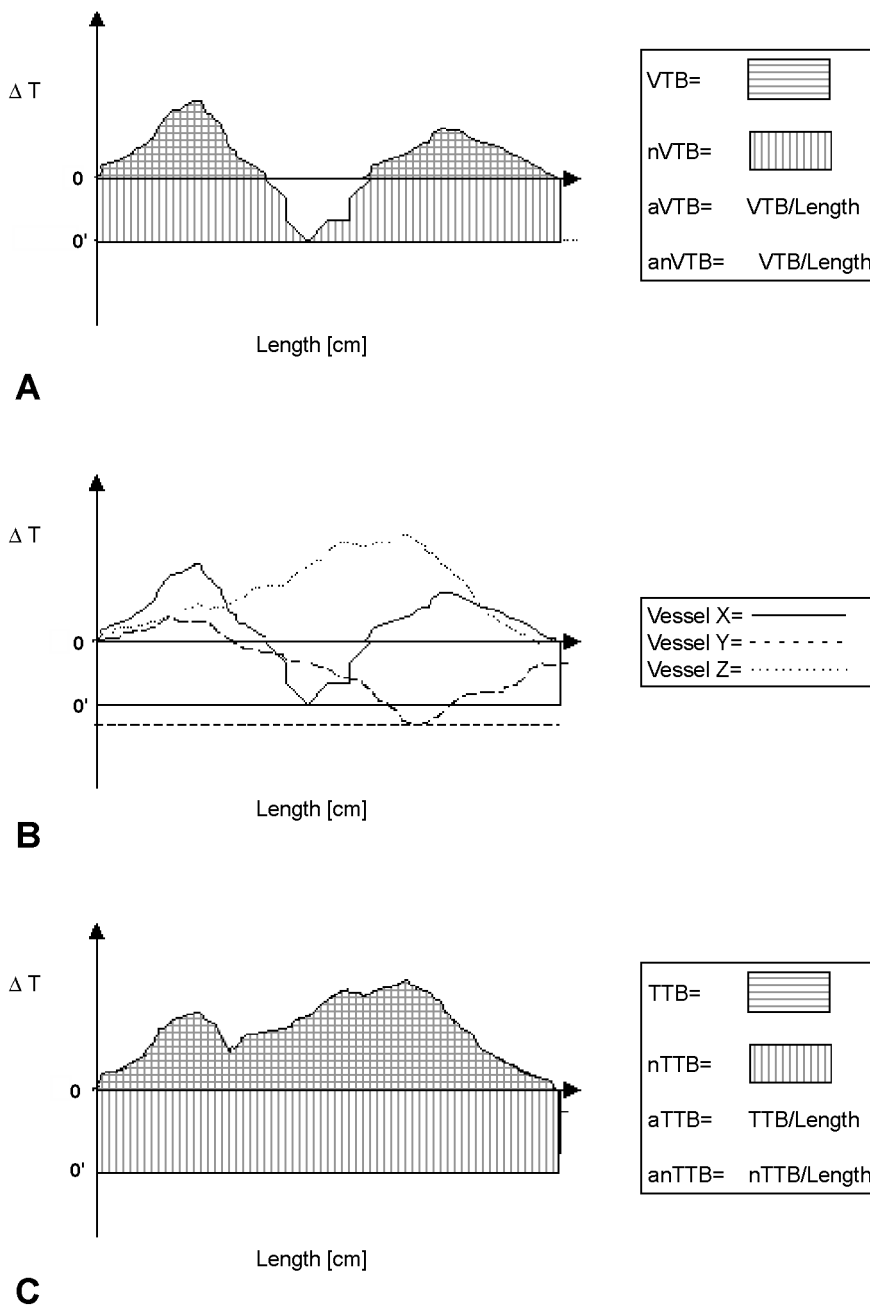
Figure 1

Figure showing a set of thermographic parameters used towards the occurrence of any cardiac event. These parameters are: (A) vessel thermographic burden (VTB or total area under the curve of all temperature increases measured for a particular vessel), normalized vessel thermographic burden (nVTB or total area under the curve of all temperature increases measured for a particular vessel, normalized for the lowest value found), vessel thermographic burden (VTB) averaged per cm of vessel (aVTB), and normalized vessel thermographic burden (nVTB) averaged per cm of vessel (anVTB); after analyzing all vessels (B), the following parameters are: (C) total thermographic burden (TTB or total area under the curve of all temperature increases measured), normalized total thermographic burden (nTTB or total area under the curve of all temperature increases measured, normalized for the lowest value found), total thermographic burden (TTB) averaged per cm of vessel (aTTB), and normalized total thermographic burden (nTTB) averaged per cm of vessel (anTTB). All the above measures will be performed with the mean temperature curve (mean from all four thermistors) and with all independent temperature curves (derived from each thermistor; including the curve that shows the highest temperature readings); 0 = the values at start of the procedure, 0' = minimum value (as per definition of 1-sided analysis).

regression covariate analysis. By definition, negative temperature values ($\beta < 0$) are non-existing. Anticipating a 'drop-out' rate (technical and clinical) of about 12%, 260 patients will be enrolled.

The safety population will consist of all patients who signed the informed consent. The primary analysis population will consist of all patients who signed the informed consent, had a (partially) successful thermography of all three vessels and who were discharged from the hospital. Additional analysis will be performed (1) per lesion; (2) correlating baseline and follow-up thermography; (3) reproducibility; (4) correlating IVUS and thermography; and (5) correlating events with location of high/low temperature. For these analyses, predefined subsets of the primary analysis population will be used.

For the prognostic analysis of thermography only events will be counted, which occurred after hospital discharge and before one-year angiographic follow-up. Count variables will be presented as a rate with its 95% confidence interval, whenever appropriate. Continuous variables will be presented as means and standard deviations with their 95% confidence interval, whenever appropriate. Differences (with respect to patient characteristics and thermographic parameters at baseline) between subgroups of patients will be evaluated by unpaired Student's t test. Both univariable and multivariable logistic regression analysis will be performed to study the diagnostic value of thermographic measurements to predict recurrence of symptoms at 12 months. Secondary analysis using multivariate Cox regression method will be performed[16]. This study will also explore

	Screening	Intervention	Discharge	1 month	6 months	Just prior to 12-month angiography	12 months
History/Events	X		X	X	X	X	
Informed Consent	X						
Physical Examination	X		X	X	X	X	
Laboratory*	X		X	X	X	X	
Electrocardiography	X		X	X	X	X	
Angiography		X					X
Thermography**		X					X

I. Populations: 1. Safety population: all patients who signed the informed consent

2. Primary analysis population: safety population plus patients who had a (partial) successful thermography and discharge from hospital.

3. Prognostic analysis population: only those events, occurring after hospital discharge and prior to 1-year angiography

II. Subgroups ($n = 15$ each): 1. Reproducibility, 2. Thermography and IVUS (baseline and follow-up), 3. Thermography (all three vessels) at years one and four. Measurement in ascending aorta.

* Troponins will be measured at six and 12 hours post procedure; ** *At baseline*: all three main epicardial vessels will undergo thermography; <u>at follow-up</u>: only one vessel will be assessed (vessel with highest thermographic burden).

Table 2

Two-dimensional schematic showing the different evaluations and time points at which they are performed.

a possible 'prognostic threshold': a cut-point in the range such that any value at or above that point would be considered as positive (i.e. characteristic of an event) and any value below as negative. Sensitivity (percent of patients with an event that does exceed the threshold— or true positive probability) and specificity (percent of event-free patients that does not exceed the threshold— or true negative probability) are calculated at each threshold.

ROC curves will also be constructed, and the area under the ROC curve will be reported, representing the diagnostic power of the variable at hand (range, 50– 100%). The pre-selected optimal threshold of a significant predictive variable will be defined as the maximum of the sum of sensitivity and specificity. With the help of this threshold, the population will be divided in two categories. The frequency of events in both categories will be determined and differences will be evaluated by χ^2 analysis. Relative risks will be reported.

Discussion

The main goal of this trial is to predict occurrence of ischemic cardiac events based on the measured temperature heterogeneity in patients presenting with acute coronary syndromes. Secondary objectives are the predictive value of high-risk plaques associated with the development of future cardiac events, the assessment of safety of the thermography procedure during initial hospitalisation, the assessment of temperature reproducibility and heterogeneity in coronary arteries, and the predictive value of a different set of thermographic parameters towards the occurrence of any cardiac event.

New imaging modalities to detect vulnerable plaque should be designed to evaluate prospectively the natural course of plaques, i.e. to detect lesions at increased risk for rupture at an early stage prior to resulting in a coronary event. So far, there have been reports on the safety and feasibility use of several imaging techniques; however, none has addressed the predictive value of such test in patients presenting with acute coronary syndromes towards future events. The vulnerable plaque is defined as a plaque that is not stenotic but with a high likelihood of becoming disrupted, thereby forming a thrombogenic focus after exposure to an acute risk factor[17]. Several factors may play a role in the propensity for rupture, but plaque composition is undoubtedly important. The histopathological correlate of the vulnerable plaque is a plaque with a lipid pool and a necrotic core, with a thin fibrous cap (between 65 and 150 μm), infiltrated by macrophages[18]. Although any plaque may rupture, the plaques that are prone to rupture have been associated with a high tensile mechanical stress within such a thin fibrous cap and a large lipid and necrotic core. None the less, not only cap thickness and mechanical forces help determining the potential to withstand the stress but also the composition of the cap: mechanical stress at the start of fracture of the fibrous caps is decreased when the cap contains macrophages[19]. This finding was underscored in a report by van der Wal *et al.*, in which the authors demonstrated that the underlying morphology of complex atherosclerotic lesions leading to acute coronary syndromes and acute myocardial infarction is heterogeneous with respect to both plaque architecture and cellular composition[20]. At sites of rupture, the authors found a high inflammatory response with an increased number of macrophages. The presence of macrophages suggests an inflammatory reaction. Indeed, atherosclerosis is an inflammatory disease and numerous factors may play a role in the induction and promotion of inflammation involving several cells including endothelial cells, monocytes as well as T-cells and their molecular and chemical end products as well as flow variations (shear stress)[5,21–24]. The production of matrix metalloproteinases, tissue factor and other sub-

stances released by apoptotic macrophages is found to be associated with plaque rupture and thrombosis[25]. We, therefore, think that intravascular thermography may offer a solution in identifying those lesions or patients at increased risk, as temperature heterogeneity is linked to inflammation.

The patients to be enrolled in this study are patients presenting with an acute coronary syndrome and thus, already experiencing thrombus formation probably associated with a vulnerable plaque. These patients show a high likelihood of having an increased event rate in the following year. In addition, it is known that these patients tend to have more than one vulnerable plaque[18,26,27]. Although this clinical study using an invasive technique to detect temperature heterogeneity in this specific patient population may be useful and provide additional value to the field of cardiology, we realize that until such results are available, both its feasibility and value will be difficult to assess.

In addition, defining a new concept of thermographic burden as a tool to predict the occurrence of future ischemic events is introduced.

Thermal burden may provide a global assessment of temperature heterogeneity within the whole coronary artery tree. We feel that thermal burden may contribute more to the understanding of the pathophysiology of the vulnerable atherosclerotic plaque than peak temperature, which may be obtained at one single, randomly chosen spot within the plaque.[8] Since coronary artery disease is an inflammatory disease, global coronary approach (assessing all three vessels) may be helpful in detecting the total 'vulnerable' burden of the vessel. As thermal burden specifically interrogates the whole segment, it may parallel the widespread inflammation that coincides with plaque/clinical instability. Demonstrating that thermal burden may have a prognostic value in predicting future events in patients demonstrating temperature heterogeneity is pursued in this study.

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