HEAT TRANSFER FROM ATHEROSCLEROTIC PLAQUES IN MULTIFOCAL CORONARY ARTERY DISEASE – A CFD MODEL

L. Rosen*, Z. Aronis*, M. Rosenfeld** and S. Einav*

*Dept. of Biomedical Engineering, Tel Aviv University, Tel Aviv, Israel
**Dept. of Fluid Mechanics and Heat Transfer, Tel Aviv University, Tel Aviv, Israel

lior@eng.tau.ac.il, zeev@eng.tau.ac.il, rosenf@eng.tau.ac.il, einav@eng.tau.ac.il

Abstract: Intravascular coronary thermography is a functional method to diagnose the presence of active inflammatory plaque that is prone to rupture. Previous in-vivo studies focused on arterial wall temperature measurement. The present study focuses on temperature distribution assessment in the proximity of the atherosclerotic lesion. A 3-D CFD model of the Left Anterior Descending (LAD) coronary artery is used to investigate the temperature distribution in two cases – single stenosis with a vulnerable plaque, and two stenoses, one with a vulnerable plaque and the other with a stable plaque, representing multi-focal coronary artery disease. The results show that significant temperature variations can be identified distal to the inflamed plaque, and not only in the near-wall region. Implications of the results to improvement of current thermography technology and to the identification of vulnerable plaques in multi-focal coronary artery disease are discussed.

Introduction

Atherosclerosis is an inflammatory disease [1]. Macrophages play an important role in atherosclerotic plaque inflammation, by secreting cytokines, growth factors, and matrix metalloproteinases (MMPs), which destabilize the plaque and promote its rupture. It is widely assumed [2] that macrophages express mitochondrial uncoupling proteins (UCP), which uncouple the electron transport chain from the process of ATP production. This results in thermogenesis, as the energy that could have been converted to ATP for body needs, is released as heat.

It is well documented that there is significant temperature heterogeneity over plaque surfaces, as inflamed lesions are hotter. It's been less than a decade since the first study regarding the prediction of thrombotic events by heat released from activated macrophages on the plaque surface or under its thin cap [3]. By measuring the intimal surface temperatures at different sites of ex-vivo human carotid artery plaques, temperature differences of 0.2 to 2.2°C have been found. It has also been shown that the temperature differences correlated positively with the density of the underlying cells (mostly macrophages), while temperature varied inversely with cap thickness.

To further investigate the subject, a thermography catheter was designed and developed for in vivo measurements of thermal heterogeneity in the human arterial system [4]. The distal tip of the intravascular catheter was equipped with accurate thermistor temperature microsensors, enabling measurement of temperature when in close contact with the vascular wall. This research included coronary artery disease patients, either with unstable angina, or with acute myocardial infarction (MI), and found that median temperature differences at the site of the lesion were increased by 1.025 °C and by 2.15 °C, respectively, from the core temperature. It has also been found that systemic markers of inflammation such as CRP (C-reactive protein) and SAA (Serum amyloid A) correlated with temperature differences, hence implying that increased local heat production of coronary atherosclerotic lesions may be due to inflammatory response.

In another research conducted by this group [5], it was demonstrated that the difference in atheromatous plaque temperature from background temperature was a strong predictor of cardiac events in patients after a successful percutaneous intervention. Moreover, a threshold of 0.5 °C has been found, above which the rate of these adverse cardiac events was significantly increased by 41%, compared with 7% in patients with $\Delta T<0.5$ºC.

Following these findings, in vivo animal study demonstrated the presence of temperature heterogeneity in hypercholestrolemic rabbits and its absence in normocholestrolemic rabbits [6]. In this study, temperature heterogeneity was reduced significantly after 3 months of cholesterol lowering, as plaque histology showed a marked loss of macrophages. Another animal model showed a thermal heterogeneity of 1.5 to 2.0 °C inside hypercholestrolemic rabbits' aorta [7].

Numerical simulations have been preformed on a model of a coronary artery segment containing a heat source [8].

The influence of heat source parameters and flow, on lumen wall temperature has been studied, and the significance of the morphologic characteristics of the atherosclerotic plaque and the flow field, on coronary thermography measurements, has been demonstrated.

A distinction between two major plaque types is acknowledged by the wide community of clinicians in the last decade: the stable plaque and the vulnerable plaque. The vulnerable plaque is most simply categorized by a fibrous cap <65 μm thick, that contains collagen and a paucity of smooth muscle cells (SMC) and a large lipid core that consists mainly of foam cells

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(macrophages laden with oxidized LDL), while a stable plaque contains a thicker fibrous cap with a pronounced presence of SMCs, and its core is mainly stabilized by a larger fibrotic and calcific content

A recent study [9], which investigated morphologic features of coronary plaque rupture, demonstrated that in 72% of cases, the minimum lumen area site was not located within the rupture site. Moreover, in 64% of them, the minimum lumen area was located distal to the rupture site, 4.2±5.8 mm from it. In another study [10], more than half of additional atherosclerotic lesions with mild to moderate stenosis were found in vessel segments proximal to the culprit lesion. These plaques had five fold higher ulceration frequency, implying that the existence of a mutifocal atherosclerotic disease may be involved in the development and rupture of a vulnerable plaque.

Hence, a study that will examine the temperature distribution in such cases may enlighten and reveal some of the mystery on multi-focal coronary artery atherosclerosis, and benefit in better design criteria of improved thermography catheters and instrumentation.

Methods

A CFD model of the left anterior descending (LAD) coronary artery was constructed, using the commercial finite-volume package Fluent 6.1.22 (Fluent Inc., Lebanon, NH). The LAD was chosen for this simulation due its significance in the left ventricle perfusion, and also as one third of coronary stenosis tend to occur in this artery [11]. The model consisted a 3-D stenosed vessel (see
Figure **1**), with length and diameter of 100 mm and 3.5 mm, respectively, corresponding to normal lumen diameter of the proximal LAD in healthy men [12]. The stenosed LAD models were investigated under a typical physiological LAD flow profile at heart rate of 70 beats per minute. The vessel walls were assumed to be rigid, neglecting wall motion effects due to coronary distensibility, which are in the order of 5±2 % change in perimeter, as previously measured [13]. The flow inside the vessel was pulsating. It is generally agreed that under physiological conditions, the Newtonian model for blood rheology can be considered acceptable for a first level approximation. For this reason, the simulations considered blood as an incompressible and Newtonian fluid. The flow was assumed to be laminar, as the mean Reynolds number in the coronary arteries is about 150 under resting conditions [14]. Blood and arterial wall properties were taken from the literature [8].

Two cases were studied – one with a 50% diameter stenosis, and a second case with an additional 70% stenosis, distal to the former one. A uniform temperature boundary condition of 39ºC was set at the 50% stenosis wall, representing acute MI conditions. The 70% stenosis was modeled as a stable plaque, and hence a boundary condition of 37ºC was set at its wall.

The flow, pressure and temperature fields in the models were calculated by solving the governing equations in the fluid domain, using finite volume methods. The governing equations of the fluid are the continuity, momentum and energy equations. The continuity equation is derived from mass conservation considerations, and may be represented per unit volume as:

$$\nabla \cdot \vec{v} = 0 \qquad (1)$$

where $\vec{v}$ is the velocity vector.

The momentum equations are derived from Newton's second law. Assuming the blood is Newtonian, incompressible and with constant viscosity, the Navier-Stokes equations are:

$$\rho\left[\frac{\partial \vec{v}}{\partial t} + (\vec{v}\cdot\nabla)\vec{v}\right] = -\nabla p + \mu\nabla^2\vec{v} \qquad (2)$$

where p is the static pressure, t is time, ρ is density, and μ is the dynamic viscosity.

The energy equation is:

$$\rho C_p \frac{DT}{Dt} = k\nabla^2 T \qquad (3)$$

where ρ is density, Cp is the heat capacity, T is the temperature and k is the thermal conductivity.

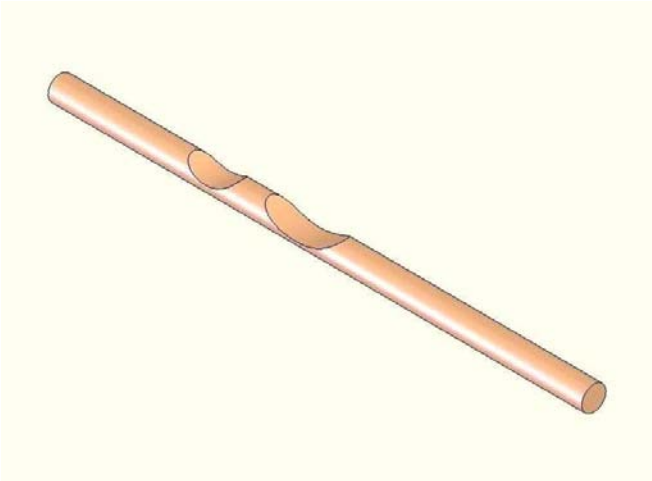

Figure 1: The 3-D model, with a proximal 50% diameter stenosis, and a distal 70% diameter stenosis.

The model was meshed by 214,000 tetrahedral elements, using Gambit (Fluent Inc., Lebanon, NH). The governing equations were solved for the domain, by discretization of the equations on the computational grid, the formulation of a set of algebraic equations, and their solution.

Results

The released heat from the arterial wall is transferred by conduction and convection to the surrounding neighborhood. Regions in which the velocity is higher contribute to faster cooling of the blood, while regions in which velocity is lower, such as the recirculation zones distal to the occlusions, are characterized with higher blood temperature. During the heart cycle, it can be seen that when the velocity is lower, e.g. in the end-

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diastole and end-systole, the heat discharge is slower, and thus the temperature at the distal region of the stenosis is higher than in the peak-systole or peak-diastole.

The temperature profile in a longitudinal cross-section at the center of the artery, during the peak diastole phase of the heart cycle, is presented in Figure 2 below, for the single vulnerable plaque case (2a), and vulnerable plaque with a distal stable stenosis, representing multi-focal coronary artery disease case (2b). It can be seen that the temperature distal to the inflamed plaque reaches about 37.5ºC. In the multi-focal case, the temperature in that area is slightly higher than in the single stenosis case, due to emphasized recirculation effects, caused by the presence of the distal plaque. A milder up-regulation in temperature can also be measured distal to the second stable stenosis, as the temperature there reaches 37.1ºC.

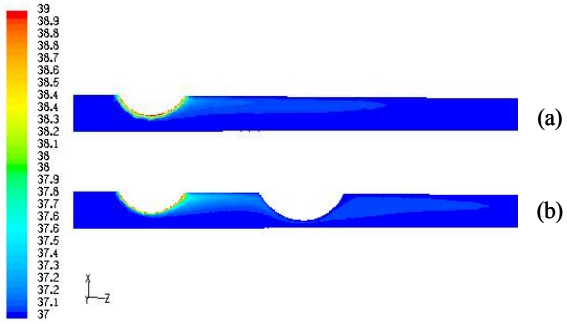

Figure 2: Temperature distribution in (a) single vulnerable plaque, and (b) vulnerable plaque with a distal stable stenosis.

The proximal shoulder of the distal stenosis, in the multi-focal case, is heated up to 0.2-0.3 °C, depending on the phase in the heart cycle, as demonstrated in Figure 3, which represents a zoomed view of that area. Figure 4 shows the cross-sectional temperature profile at a distance of 0.5mm proximal to the distal stenosis in both cases, single and multi-focal plaque disease. The peak temperature in the case with two stenoses is higher by 0.15 °C compared to a case with a single stenosis.

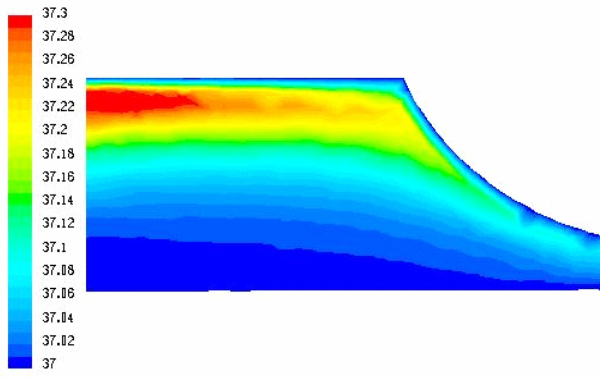

Figure 3: Zoomed view of the temperature distribution at the proximal shoulder of the distal stable stenosis.

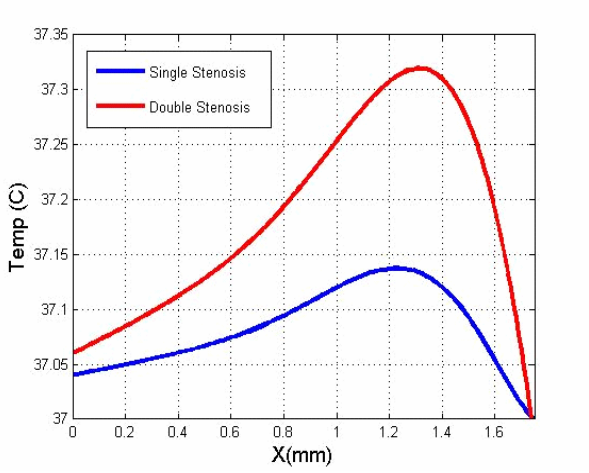

Figure 4: Blood temperature at Z=35mm, 0.5 mm proximal to the distal stenosis.

Discussion

Current thermography studies focus on arterial wall temperature as a marker of atherosclerosis. Different kinds of catheters were developed in order to map temperature distributions along blood vessels in vivo, all of which are equipped with thermistors or thermocouples that come in contact with the blood vessel wall to follow its contour while pulled backwards along a guidewire.

The results of the present study demonstrate how by broadening current methods, searching for blood temperature variations in the coronary arteries, and in particular the temperature levels distal to inflammatory-suspicious areas, may benefit in locating vulnerable plaques.

In multi-focal coronary artery disease, when the vulnerable plaque is usually the proximal one, the wake of higher temperature is longer than compared with cases with only one stenosis, in the same level of severity. The wake's length changes over the course of a cycle from systole to diastole. The flow of the coronary arteries is maximal at the diastolic phase and not at the systolic phase, because of their location in the myocardial muscle, which contracts at peak systole. The heart's contraction imposes larger flow resistance because it shrinks the coronary arteries as well, so the higher flow is in the relaxation phase – during diastole. Therefore, a longer jet is produced during the diastolic phase, when the flow is larger. However, at the systolic phase the temperature values that can be measured in the wake are higher – and it is expected since in the shorter wake the temperature is less dispersed

The fact that the area proximal to the shoulder of a stable plaque, located distal to a vulnerable inflamed plaque, is heated up, might not be identified, if following conventional thermography procedures that focus only on the arterial wall temperature. For instance, the wall temperature of the distal stable stenosis remains constant (37ºC), despite the fact that higher temperature regions exist in its proximity. By measuring the blood temperature in near-wall regions, as well as in other sites of the artery, heat release attributed to an

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inflammation in proximal plaques, which may be not visible angiographically, can be detected. An upregulation in the order of 0.15 °C in the proximity of the shoulder of the distal plaque in a multi-focal case, for example, can be missed entirely when conventional methods are in use.

It can also be hypothesized that the length of the temperature wake region, distal to the stenosis would correlate with the stenosis severity and the source of inflammation. Finding such correlation, by mapping various case studies with different boundary conditions, can assist in evaluating coronary thermography measurements' results and better interpretation of their clinical implications.

One of the characteristic features of a vulnerable plaque is the absence of severe narrowing, therefore reducing the velocity values and the distance of the distal temperature distribution (compared with stable plaques with severe stenosis). On the other hand, vulnerable plaques seem to possess severer inflammatory processes and are capable of generating higher wall temperatures than stable and highly stenotic plaques. Hence, it seems that the total heat flux in the vicinity of the plaque will depend on a balance between the plaque geometry and the degree of inflammation within

The results of this study emphasize the need and the potential benefits of new designs of thermography catheters, having spatial thermistor configuration, enabling measurement of temperature variations in various cross sections of the artery.

Conclusions

The vulnerable highly-inflamed atherosclerotic plaque is hard to detect by conventional imaging techniques, and the current dash is after new modalities that will enable it's localization by focusing not only on its morphologic characteristics but also relying on its cellular activity and its consequences. The present work demonstrates the potential contribution of heat released from inflamed coronary plaques to temperature up-regulation downstream. These temperature variations can indicate the location and severity of the inflammation of atherosclerotic coronary plaques. The phenomena is more pronounced in multi-focal coronary disease, when there is more than one narrowing of the coronary artery due to atherosclerotic stenoses, as the temperature in the proximity of the distal stenosis is higher, and the temperature wake region is longer.

These results may open new possibilities for the detection and assessment of vulnerable plaques in coronary thermography measurements. The multi-focal plaque case study emphasizes the importance of measuring the blood temperature in the neighborhood of the atherosclerotic lesion. Such measurements can imply of other close and more inflamed plaques, and may benefit in the detection of proximal, non-angiographically visible, vulnerable plaque.

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