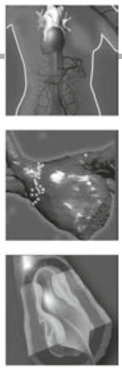

Microwave imaging to identify rupture-prone plaques: a discipline 'hotting up'

"*The application of microwave radiometry in the clinical setting in order to prevent ischemic strokes due to carotid atheromatosis has certain advantages and disadvantages. The technological improvement of the current device is mandatory in order to proceed with large prospective studies.*"

KEYWORDS: intravascular thermography ▪ microwave radiometry ▪ vulnerable plaque

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Background

Ischemic stroke is the most common form of cerebrovascular event and the main substrate is atherosclerosis. Even mild carotid artery stenosis has been found to lead to such an event, necessitating the need for identifying these atherosclerotic plaques and their high-risk features.

For the identification of high-risk plaques, intravascular thermography has been used in order to detect thermal heterogeneity (ΔT) among the atherosclerotic plaques. However, as intravascular thermography is an invasive tool, it cannot be used for primary prevention, and thus, noninvasive tools are emerging. Microwave radiometry (MR) has been previously used for detecting breast cancer tumors with high accuracy. Recently, MR was applied in an atheromatic experimental model in order to measure plaque temperature. Lately, MR has been used *in vivo* in atherosclerotic plaques in human carotid arteries, and the temperature differences found were well correlated with echocardiographic and histological findings. Several potential clinical implications of this method are discussed in this article.

"Creativity is not the finding of a thing, but the making something out of it after it is found."
– James Russell Lowell (1819–1891)

MR detects radiation that is emitted from tissues and enables the noninvasive measurement of subsurface temperature, with some imaging capability [1]. Microwave imaging has been applied in medicine since the 1970s when it was used for cancer screening and diagnosis. Nonetheless, it took scientists almost 40 years to use it as a diagnostic tool in cardiology and more than 10 years to help identify rupture-prone plaques, known as vulnerable plaques, which are implicated in causing acute coronary syndromes [2].

Vulnerable plaque & the quest for detecting it

A vulnerable plaque is defined as a plaque that is prone to rupture, and, compared with a ruptured plaque, it has a smaller lipid core of <65-μm cap thickness, less macrophage infiltration and less calcification [3]. Previous *ex vivo* studies [4] showed that rupture-prone plaques released heat owing to activated macrophages and exhibited ΔT, since there was a temperature variation along the carotid artery. Relying on this finding, Stefanadis *et al.* performed the first *in vivo* intravascular study of coronary arteries using a dedicated catheter and found temperature differences between atherosclerotic plaque and healthy vessel wall that were increased progressively from stable angina patients to patients suffering acute myocardial infarction [5]. Furthermore, another prospective study found that temperature difference between the atherosclerotic plaque and the healthy vessel wall was a strong predictor for cardiac events following percutaneous coronary intervention [6]. In order to decrease potential confounding due to the blood's 'cooling effect' [7], which previously caused underestimation of the temperature measurement, a new thermography catheter was introduced [8]. The method of intravascular thermography (IVT) has so far been the only invasive method for the assessment of ΔT of an atheromatic plaque. However, invasive diagnostic tools, such as optical coherence tomography, that are able to detect the vulnerable plaque and its characteristics [9] are not used for primary detection, therefore making it difficult for detecting rupture-prone plaques prior to an acute coronary event. On the contrary, noninvasive imaging modalities had not been favored for vulnerable plaque detection until now, owing to their low resolution and inability to detect the plaque's characteristics.

MR

MR is a noninvasive method of measuring natural electromagnetic radiation from internal tissues at microwave frequencies, and the intensity of the radiation is proportional to the temperature of the tissue. All tissues with a temperature above absolute zero emit electromagnetic energy, thus enabling measurement of the internal temperature of human tissues. A vital difference between MR and IVT is the noninvasive nature of MR, as well as that with MR, there is no radiation involved in the procedure [10].

Recently a device has been developed that is able to measure electromagnetic radiation at microwave frequencies. This device is composed of an antenna that has two sensors, a microwave and an infrared sensor, and the main processing unit. The antenna also has a sensor that filters all microwaves or radiofrequency waves that may be present in the room area and may interfere with the measurements. The measurements are displayed as a temperature map, in which cool areas of the vessel are displayed by 'cold' colors (i.e., blue) and hot ones are reflected by 'warm' colors (red and orange).

Experimental application of MR

The experimental study of MR was performed in an experimental hypercholesterolemic model and was the first to assess MR *in vivo*. During this study, MR and IVT were performed in experimental rabbits and ΔT was detected by both methods. MR and IVT measurement had a good correlation and MR demonstrated a high reproducibility. Moreover, MR addressed the main limitation of IVT, the 'cooling effect' of blood flow, and the MR temperature values approximated the *ex vivo* measurement of Casscells *et al.* [4,7]. The histological analysis demonstrated that thicker atheromatic plaques had higher ΔT, as assessed by both methods. Furthermore, atherosclerotic segments with higher temperatures compared with non-atherosclerotic segments had higher concentrations of mast cells, lymphocytes and immunohistological factors such as CD3 and CD68.

The main results of the study were: first, that MR can be safely applied for the noninvasive measurement of the arterial wall temperature, and second, that the temperature measurements obtained by MR correlate well with the measurements of IVT and the local inflammatory activation as seen by histology [11].

In vivo application in human carotids

After demonstrating the safety and effectiveness of MR in the experimental model, we investigated whether temperature differences can be measured noninvasively *in vivo* by MR in patients with carotid artery disease who are planed for endarterectomy. In addition, the possible correlation between temperature findings and ultrasound and histological findings was studied [12]. All patients (n = 34) as well as the control group (n = 15) underwent carotid artery ultrasound scans and MR measurement. After endarterectomy, the atherosclerotic plaques were prepared for histological and immunohistochemical study.

Patients with fatty or mixed plaques had higher ΔT compared with the control group, as had patients with ulcerated plaques. The histological findings were in accordance with the ultrasound findings. Atherosclerotic plaques with an extended lipid core, increased inflammatory infiltrate and ≤200-μm cap thickness had all increased ΔT. Furthermore, patients with increased ΔT showed an increase in CD3, a macrophage marker, CD68, a lymphocyte marker and VEGF, a neoangiogenesis marker.

Several studies suggest that patients with carotid artery disease and vulnerable atherosclerotic plaques have worse prognosis compared with patients with stable plaques [13,14]. Currently, there is no modality for the noninvasive and *in vivo* imaging of the vulnerable plaque's characteristics and the invasive modalities cannot be used for primary prevention. The results of this study are promising regarding the use of a simple and noninvasive method for the primary prevention of stroke.

The application of MR has definite limitations that can be eliminated with the improvement of the device's dimensions. The main problems are the overlapping of the measurements and the possible impact of other tissues, except of the vascular wall, on temperature recordings. The improvement of technology, which will provide focused measurements in specific depths, guided by ultrasound, could definitely be a solution. Moreover, a possible increase in the depth of the measurement could lead to MR application in deeper tissues.

Clinical implications

The current evidence suggests that MR can provide information regarding local inflammatory activation in carotid atheromatic plaques.

Whether MR measurements can be an additive tool for the primary prevention of ischemic stroke needs to be investigated. Moreover, the noninvasive mode of the method permits its safe and easy application in other organs for the measurement of local temperature. The results of the preliminary observation justify the performance of studies with MR in several disease states, such as myocarditis and acute myocardial infarction.

Conclusion

Several methods have been applied in the last decade in order to detect the high-risk or vulnerable plaque in the carotids and coronary arteries. None of the currently available methods can solely provide prognostic information with definite clinical implications. The application of MR in the clinical setting in order to prevent ischemic strokes due to carotid atheromatosis has certain advantages and disadvantages. The technological improvement of the current device is mandatory in order to proceed with large prospective studies.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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