

# Atherosclerotic plaque inflammation quantification using dynamic contrast-enhanced (DCE) MRI

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**Abstract:** Inflammation plays an important role in atherosclerosis. Given the increasing interest in using in-vivo imaging methods to study the physiology and treatment effects in atherosclerosis, noninvasive intraplaque inflammation quantitative method is needed. Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) has been proposed and validated to quantitatively characterize atherosclerotic plaque inflammation. Recent studies have optimized the imaging protocol, pharmacokinetic modeling techniques. All of these technical advances further promoted DCE-MRI to clinical investigations in plaque risk assessment and therapeutic response monitor. Although larger clinical studies are still needed, DCE-MRI has been proven to be a promising tool to reveal more about intraplaque inflammation by *in vivo* quantitative inflammation imaging.

**Keywords:** Atherosclerosis; dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI); plaque inflammation quantification



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Atherosclerosis, a systemic disease of arteries, is the primary cause of heart disease and stroke and the underlying cause of about 50% of all deaths in westernized societies (1). Inflammatory mechanisms are critical for the whole process of atheroma formation (2). Atherosclerosis is initiated with inflammatory cell infiltration. The development of foam cells is the basis for necrotic core formation. Moreover, disruption of plaque and generation of thrombosis, which lead to myocardial infarctions and most strokes, are promoted by inflammatory pathways (2). Thus, quantitative plaque inflammation imaging may contribute to identification of high-risk patients and understanding the benefits of new anti-atherosclerosis therapies.

Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) is considered a convenient and powerful technique to quantitatively characterize atherosclerotic plaque inflammation. The physiological basis of DCE-MRI is that inflammation stimulates angiogenesis and the leaky neovasculature is a major route for inflammatory

cell infiltration as well as the major route for contrast agent enhancement and clearance. By pharmacokinetic modeling, the contrast dynamic behavior in plaque, the neovasculature and its permeability can be quantified to characterize intra-plaque inflammation. Previously, our studies (3-6) demonstrated the feasibility of DCE-MRI in plaque inflammation quantification with pharmacokinetic analysis. Researchers started to investigate plaque changes in longitudinal studies (6-8). The imaging and analyzing protocols are, however, still under development and some critical information remains largely unknown to promote DCE-MRI for clinical investigations such as the inter-scan reproducibility.

In the Jan. 2013 issue of *Radiology*, Gaens *et al.* (9) investigated DCE-MRI for plaque inflammation quantification in three aspects: model selection, reproducibility and validation. The distinguishing contribution of this work is their effort to find a proper technical solution for plaque DCE-MRI, and to report the inter-scan reproducibility in

human population. First, they found that the Patlak model (10) has significant lower mean relative fit uncertainty among four known pharmacokinetic models. This result supports our experiences (3-6) to use the same pharmacokinetic model. We also found lower variability with the Patlak model in Chen *et al.* (11), but at a possible cost of greater bias. Notably, pharmacokinetic model selection not only depends on the accuracy of the model but also relies on imaging protocol and characteristics of the targeted tissue. Unlike the application in brain and tumor imaging, vessel wall imaging targets a much smaller region of interest (ROI). The critical need for high spatial resolution leads to a relative low temporal resolution. Such characteristics of their vessel wall DCE-MRI protocol should be the reason for preference for the Patlak model in this study. Further development of fast imaging techniques would improve the temporal resolution of DCE-MRI (12), which may affect model selection in the future.

Gaens *et al.* (9) also validated DCE-MRI in intra-plaque inflammation quantification again by demonstrating a strong positive correlation between pharmacokinetic parameter (the transfer constant,  $K^{trans}$ ) and endothelial micro vessel content in histology. Kerwin *et al.* (3-5) likewise found an association between kinetic parameters and vascular content. Moreover, Kerwin *et al.* and Chen *et al.* found  $K^{trans}$  was correlated with another inflammation biomarker: macrophages (4-6). These studies indicated the ability of DCE-MRI in inflammation and angiogenesis quantification. Another important contribution of Gaens *et al.* (9) is to report the inter-scan reproducibility of pharmacokinetic parameters derived from DCE-MRI in human subjects. This information is critical for the sample size estimation in clinical trial design. We reported the reproducibility of pharmacokinetic parameters in animal models in Chen *et al.* (6) and in patients using different contrast agents in Kerwin *et al.* (13). By reporting the reproducibility for patients, Gaens *et al.* (9) further promoted DCE-MRI to clinical researches. Further investigations in a multi-center setting are, however, still needed for large clinical trials.

Like most previous DCE imaging studies of the human carotid artery, Gaens *et al.* (9) only included arteries with advanced lesions. In contrast, to understand plaque progression/regression for early diagnosis and treatment, early lesions are also valuable to be investigated. However, the bright-blood imaging techniques used in Gaens *et al.* (9) and other studies (3-5) preclude the evaluations of thin vessel walls due to signal contamination from high intensity lumen. For the same reason, some key regions where inflammation plays a role in plaque rupture, such as

the fibrous cap and shoulder regions (14), cannot be clearly delineated in bright-blood protocol. Another technical limitation is the low temporal resolution which introduces bias in pharmacokinetic analysis, especially for arterial input function (AIF). Finally, the assumed T10/T20 in contrast concentration calculation may also introduce bias, considering that plaques have complex components (14) (necrotic core, intra-plaque hemorrhage, calcification, etc.).

Many researchers spend their efforts in further improving the DCE-MRI imaging and analysis protocol of vessel wall. Calcagno *et al.* (15) proposed “black-blood” technique for vessel wall DCE imaging in animal models, which provides a possible solution for early lesion characterization. The area under the contrast enhancing curve (AUC) rather than pharmacokinetic parameters was, however, used in most studies with black-blood DCE-MRI protocol (16-19) due to the difficulties in measuring AIF. Recently, our study (6) used a reference region based method in pharmacokinetic analysis without explicitly acquiring AIF to obtain parameters with physiological meaning in black-blood DCE-MRI. Furthermore, to improve the accuracy of pharmacokinetic analysis, interleaved acquisition imaging method (20) and parallel imaging method (21) were proposed to improve the temporal resolution in vessel wall DCE MR imaging.

With the wide acknowledgement of the importance of inflammation in atherosclerosis, many imaging techniques other than DCE-MRI have been used for *in vivo* intra-plaque inflammation imaging, especially the molecular imaging methods. Targeted contrast agents for inflammation were proposed in MRI (22,23), ultrasound (24,25), and positron emission tomography (PET) (26,27). Only a few have been approved for clinical studies involving patients, including 18F-fluorodeoxyglucose (FDG) PET (26), micro-bubbles enhanced ultrasound (24), ultrasmall superparamagnetic iron oxides (USPIOs) enhanced MRI (28). Notably, all these *in vivo* imaging techniques do not image inflammation directly. FDG PET measures the metabolic activity, utilizing the fact that macrophages have much higher metabolic rate than other cells. Micro-bubbles are introduced into plaque through the neovasculature by perfusion and can be visualized through ultrasound. USPIOs rely on the macrophages phagocytosis residing in plaque so that they can be imaged after a long period (usually more than one day) of administration. Compared with these techniques, DCE-MRI has some unique advantages. First, the imaging procedure is convenient and fast, that can be finished with 4-7 min in

one scan without ionizing radiation. The clinically available gadolinium contrast agents have a good safety record after excluding patients with insufficient renal functions. More importantly, MRI has a high spatial resolution (around 0.5 mm) that allows localized measurements (6,29). Recent technical advancements of black-blood DCE-MRI (6) may solve the inflammation quantification in early lesions and, finally, the fibrous cap and shoulder regions in advanced plaque where inflammation leads to rupture (14).

All these *in vivo* imaging techniques, including DCE-MRI, image different functional aspects of inflammation rather than quantify inflammation directly as autopsy. All of them, however, can provide information that cannot be observed in histological studies. Take FDG PET and DCE-MRI as examples. The presence of macrophages alone observed in histological slices may not trigger a high FDG uptake *in vivo* (30); while the permeability of plaque neovessels measured by DCE-MRI cannot be simply quantified in *ex vivo* specimens. Recent studies revealed a weak positive (31), even negative correlation (32) between FDG PET and DCE-MRI, suggesting that they are measuring independent aspects of plaque inflammation. Moreover, plaque inflammation has a dynamic nature (33) that can only be observed *in vivo* by imaging methods rather than histological analysis.

Overall, the main purpose of *in vivo* intra-plaque inflammation imaging is to provide a clinical tool for vulnerable plaque identification, to better understand the role of inflammation and angiogenesis in plaque progression/regression, and to monitor therapeutic response. Intensive lipid lowering therapy has recently been found to affect the carotid vasa vasorum by using DCE-MRI (8), and has proven the ability of DCE-MRI in longitudinal studies. Moreover, perfusion characterization has been reported to increase earlier than morphological changes during the natural progression of experimental lesions (6). Finally, intra-plaque hemorrhage, an indicator of high risk, was found to be associated with DCE-MRI measurements (34). These studies suggest that DCE-MRI is a promising inflammation quantification tool in clinical research of atherosclerosis. Larger longitudinal studies are needed to further investigate the clinical significance of *in vivo* inflammation imaging. The study performed by Gaens *et al.* (9) makes DCE-MRI closer to clinical application and research.

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