Neovascularization in Vertebral Artery Atheroma—A Dynamic Contrast-Enhanced Magnetic Resonance Imaging-Based Comparative Study in Patients with Symptomatic and Asymptomatic Carotid Artery Disease

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Background: Atherosclerosis is a systemic inflammatory disease intertwined with neovascularization. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) enables the assessment of plaque neovascularization. This study aimed to explore the systemic nature of atherosclerosis by assessing difference in severity of neovascularization as quantified by DCE-MRI of vertebral arteries (VAs) between patients with symptomatic and asymptomatic carotid artery disease. *Methods:* Ten consecutive patients with asymptomatic VA stenosis and concomitant symptomatic carotid artery disease (group 1) and 10 consecutive patients with asymptomatic VA stenosis and concomitant asymptomatic carotid artery disease (group 2) underwent 3-dimensional DCE-MRI of their cervical segment of VAs. A previously validated pharmacokinetic modeling approach was used for DCE-MRI analysis. K^{trans} was calculated in the adventitia and plaque as a measure of neovessel permeability. *Results:* Both patient groups were comparable for demographics and comorbidities. Mean luminal stenosis was comparable for both groups (54.4% versus 52.27%, $P = .32$). Group 1 had higher adventitial K^{trans} and plaque K^{trans} ($.08 \pm .01$ min^{-1}, $.07 \pm .01$ min^{-1}) compared with Group 2 ($.06 \pm .01$ min^{-1}, $.06 \pm .01$ min^{-1}) ($P = .004$ and .03, respectively). Good correlation was present among the two image analysts (intraclass correlation coefficient = .78). *Conclusions:* Vertebral Artery atheroma of patients with symptomatic carotid artery disease had increased neovessel permeability compared with the patients with asymptomatic carotid artery disease. These findings are consistent with the hypothesis that atherosclerosis is a systemic inflammatory disease. The VA atherosclerosis is likely to have increased severity of neovascularization if another arterial territory is symptomatic in the

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Received April 12, 2018; accepted May 6, 2018.

Grant support: This study was supported by NIHR and Biomedical Research Centre award to the Cambridge University Hospitals NHS Foundation Trust. A.U. is funded by Mountbatten Cambridge International Scholarship in collaboration with Cambridge Trust, Christ's College, and Sir Ernest Cassel Educational Trust.

Disclosures: None.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.05.011

same patient cohort. **Key Words:** Atheroma—plaque—magnetic resonance imaging—neovascularization—vasa vasorum—dynamic contrast-enhanced MRI—vertebral artery.

Introduction

Atherosclerosis is a systemic inflammatory disease with plaque inflammation and neovascularization as the key predictors of plaque rupture and thromboembolic events.[1] Because of the systemic nature of atherosclerotic disease process, more than 1 arterial bed may be affected simultaneously. With the advancement in understanding the pathobiology of atherosclerosis,[2,3] there has been a paradigm shift from luminal stenosis to the morphological and underlying pathophysiological functional assessment of atheromatous lesions, as novel indicators of the atherosclerotic disease severity. This has paved the way for the development of functional magnetic resonance imaging (MRI) modalities to identify the plaque neovascularization and quantify the inflammatory burden within plaque. Dynamic contrast-enhanced MRI (DCE-MRI) is one of the imaging techniques that has been successfully used for the functional assessment of carotid atheroma by allowing quantification of permeability of neovessels.[4] This is most commonly expressed in terms of K^{trans}, which is the intravascular to extravascular (contrast media) transfer constant, and the average K^{trans} within the adventitia represents the quantitative assessment of extent of vasa vasorum. The DCE-MRI quantified neovessel permeability has been shown to have strong correlation histologically with neovessel count and the associated inflammatory burden.[5] This technique is repeatable and reproducible.[6]

Approximately 25% of the thromboembolic events occur in the vertebrobasilar territory.[7] Extracranial vertebral artery (VA) stenosis involving the origin and V1 segment constitutes 9% of the posterior circulation stroke or transient ischemic attacks (TIAs).[8,9] Despite being a significant cause of stroke/TIA, the prevalence of VA stenosis in patients with asymptomatic disease is not well established. The proximal VA is difficult to insonate. Duplex ultrasound has been observed to have low sensitivity and failure to identify most of the VA stenoses.[10] In clinical practice, duplex imaging is usually used for assessing the direction of blood flow in the VAs and for indirect assessment of VA stenosis by calculating the velocity increase across a stenosis. Imaging modalities such as high-resolution MRI have been successfully used for vessel wall imaging of the vertebrobasilar circulation.[11-13] However, these reports have mainly focused on morphometric assessment of atheromatous plaques. The functional assessment of the VA plaque pathophysiology remains widely unexplored.

Because most of the patients with VA atherosclerosis remain asymptomatic or eventually become symptomatic with more lethal consequences such as cerebral or brainstem ischemia leading to severe morbidity or death, it is important to identify those patients at high risk for significant VA disease and plaque rupture to help in risk-stratification and decision-making.

The aim of this study is to evaluate the feasibility of 3-dimensional (3-D) DCE-MRI in assessing neovascularization in VA atheroma and to explore the difference in the degree of magnetic resonance (MR)-defined neovascularization in vertebral territory in patients with concomitant symptomatic or asymptomatic carotid artery disease. The hypothesis is that 1 inflamed symptomatic vascular bed (carotid) is likely to increase the risk of other arterial vessels to become inflamed (vertebral territory).

Methods and Materials

Study Population

Ten consecutive patients with asymptomatic VA stenosis and concomitant symptomatic carotid artery disease (group 1) and 10 consecutive patients with asymptomatic VA stenosis and concomitant asymptomatic carotid artery disease (group 2), with duplex-identified extracranial vascular disease, underwent DCE-MRI of their cervical segment of VAs. The local research ethics committee approved this study. All the subjects gave written informed consent.

The inclusion criteria for this study were as follows:

- Male or female aged 18-90 years of age
- Arterial duplex confirmed extracranial disease

The exclusion criteria were as follows:

- Contraindication to MRI, including intracranial aneurysm clips, intra-orbital metal fragments, pacemakers and non-MR compatible heart valves, inner eyes implants
- History of claustrophobia
- History of allergy to gadolinium
- Inability to give informed consent

MRI Protocol

Imaging was performed on a 3T MRI system (MR750, GE Healthcare, Waukesha, WI), using a 4-channel phased-array neck coil (PACC, MachNet, Roden, The Netherlands). 3-D time-resolved imaging of contrast kinetics (flip angle, 20°; echo time/repetition time [TE/TR], 1.5/3.9 ms; field of view, $140 \times 140 \times 62$; matrix, $224 \times 224 \times 44$) was performed to acquire both DCE and contrast-enhanced