Neovascularization in vertebral artery atheroma- a dynamic contrast enhanced MR Imaging based comparative study in patients with symptomatic and asymptomatic carotid artery disease.

Running Title

DCE MR Imaging of vertebral atheroma neovascularization

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Abstract

Background:

Atherosclerosis is a systemic inflammatory disease intertwined with neovascularisation. Dynamic contrast-enhanced magnetic resonance (DCE-MR) imaging enables the assessment of plaque neovascularisation. This study aimed to explore systemic nature of atherosclerosis by assessing difference in severity of neovascularisation as quantified by DCE-MR imaging of vertebral arteries (VA) between patients with symptomatic and asymptomatic carotid artery disease.

Methods:

10 consecutive patients with asymptomatic vertebral artery stenosis and concomitant symptomatic carotid artery disease (group 1); and 10 consecutive patients with asymptomatic vertebral artery stenosis and concomitant asymptomatic carotid artery disease (group 2), underwent 3D DCE-MRI of their cervical segment of vertebral arteries. A previously validated pharmacokinetic modelling approach was used for DCE-MR 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 co-morbidities. Mean luminal stenosis was comparable for both groups (54.4% vs 52.27%, p= 0.32). Group 1 had higher adventitial K^{trans} and plaque K^{trans} ($0.08 \pm 0.01 min^{-1}$, $0.07 \pm 0.01 min^{-1}$ compared to Group 2 (0.06 ± 0.01 min^{-1}, $0.06 \pm 0.01 min^{-1}$), (p =0.004 and 0.03) respectively. Good correlation was present among the two image analysts (ICC coefficient=0.78).

Conclusions

Vertebral artery atheroma of patients with symptomatic carotid artery disease had increased neovessel permeability compared to the patients with asymptomatic carotid artery disease. These findings are consistent with the hypothesis that atherosclerosis is a systemic inflammatory disease. The vertebral artery atherosclerosis is likely to have increased severity of neovascularisation if another arterial territory is symptomatic in the same patient cohort.

Keywords: atheroma; plaque; magnetic resonance imaging; neovascularisation; vasa vasorum; dynamic contrast enhanced MRI; vertebral artery

Abbreviations list:

Vertebral artery (VA), Transient ischemic attacks (TIAs), Magnetic resonance (MR), Dynamic contrast enhanced magnetic resonance (DCE-MR), Time-resolved imaging of contrast kinetics (TRICKS); region of interest (ROI); European Carotid Surgery Trial (ECST); image quality (IQ); Vasorum Imaging (VVI); Kalman Filtering Registration and Smoothing (KFRS); plaque haemorrhage (PH); interquartile range (IQ)

Introduction

Atherosclerosis is a systemic inflammatory disease with plaque inflammation and neovascularisation as the key predictors of plaque rupture and thromboembolic events[1]. Due to the systemic nature of atherosclerotic disease process, more than one 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 modalities to identify the plaque neovascularization and quantify the inflammatory burden within plaque. Dynamic contrast enhanced MR imaging (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 extra vascular (contrast media) transfer constant and the average K^{trans} within the adventitia represents the quantitative assessment of extent of vasa vasorum. The DCE-MR 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 occurs 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 magnetic resonance (MR) imaging 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 the VA plaque pathophysiology remains widely unexplored.

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

The aim of this study is to evaluate the feasibility of 3D DCE-MRI in assessing neovascularization in vertebral artery atheroma and to explore the difference in the degree of MR defined neovascularization in vertebral territory in patients with concomitant symptomatic or asymptomatic carotid artery disease. The hypothesis is that one 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

10 consecutive patients with asymptomatic vertebral artery stenosis and concomitant symptomatic carotid artery disease (group 1); and 10 consecutive patients with asymptomatic vertebral artery stenosis and concomitant asymptomatic carotid artery disease (group 2), with

duplex identified extracranial vascular disease, underwent DCE-MR imaging of their cervical segment of vertebral arteries. The local research ethics committee approved this study. All the subjects gave written informed consent.

The inclusion criteria for this study were:

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

The exclusion criteria were:

- Contraindication to MR imaging 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

MR imaging protocol:

Imaging was performed on a 3T MR Imaging system (MR750, GE Healthcare, Waukesha, WI), using a 4 -channel phased-array neck coil (PACC, MachNet, The Netherlands). Three-dimensional (3D) time-resolved imaging of contrast kinetics (TRICKS) (flip angle, 20°; TE/TR, 1.5/3.9ms; field of view, 140x140x62; matrix, 224x224x44) was performed to acquire both DCE and CE-MRA of the cervical segment of both vertebral arteries. Acquisition time was 6 min 23s, to obtain a mask image and 30 temporally interpolated phases with a temporal resolution of 10.6s. Coincident with the third phase, a bolus of

0.1mmol/kg Gd-DPTA (Gadovist, Bayer Schering, Berlin, Germany) was administered intravenously with an MR-compatible power syringe at a flow rate of 3mL/s followed by a 20ml saline flush. The CE-MRA data was obtained by subtracting the baseline scan from the multi-phase acquisition.

In addition following sequences were used for morphometric assessment of VA wall: pre- and post-contrast 3D T_1w DANTE-prepared fast spin echo[14] (variable flip angle; TE/TR 16.9/540; field of view 140x140x67; matrix, 224x224x48 acquisition time,2x6min 26s), (DANTE-black blood using delays alternating with nutation for tailored excitation), 3D time of flight (TOF) (Flip angle,20^{o};TE/TR 2.2/5.9ms; field of view, 140x140x64mm; matrix,256x256x32;acqusition time,1min35s).

Image analysis:

The T_1w and DCE images were reformatted into the axial plane with a 0.7mm slice thickness using an Advantage Workstation (version 4.6, GE Healthcare, Waukesha, WI) (Fig I). For each patient, VAs of both sides was analysed. On average 15-20 axial slices per side per patient were analysed. Inner and outer-wall contours were drawn manually, thereby determining the vessel wall region of interest (ROI) at each slice according to the multi-contrast images, using the OsiriX DICOM viewer (version 5.5.2, PixmeoSari, USA) (shown in figure I). Vessel wall and lumen boundaries were mainly based on pre-contrast T_1w images. The subtracted CE-MRA image at the fifth phase, which has highest contrast of the VA, were used for analysis. Vessel wall area was calculated as a difference between lumen area and total vessel wall area using 3D DANTE CUBE sequence. Luminal stenosis was measured for each plaque using European Carotid Surgery Trial (ECST) criteria[15]. 70% of the retrieved images were of sufficient quality according to the set five-point scale (1=poor, 5=excellent), to be used for quantitative analysis. The image quality (IQ) was rated by

previously published five-point scale[16]. Images with IQ> 3 were included for morphological analysis while images with IQ>4 were included for quantitative analysis. Four patients with image quality score less than 3 were excluded.

Pharmacokinetic Modelling

Images from the acquired data were processed using University of Washington (Seattle) Vasa Vasorum Imaging (VVI) tool[17]. This approach firstly applies a Kalman Filtering Registration and Smoothing (KFRS) algorithm, to reduce noise level in the image and correct patient motion [18]. A two-compartment Patlak model[19] is then used to generate a parametric map known as the "vasa vasorum image (VVI)" showing partial plasma volume (v_p) in shades of red and transfer constant (K^{trans}) in shades of green (Figure II). The relationship between blood and tissue signal concentration is modelled as follow

$$C_t(t) = v_p C_p(t) + K_{trans} \int_0^t C_p(t')dt'$$

In this equation C_t and C_p represent the contrast agent concentration in the tissue and blood plasma, respectively[17]. Lumen and wall boundaries manually segmented from T_1w images were copied to the VVI. Adjustment was performed if necessary to ensure the lumen contour encloses the red region and wall boundary is overlaying the rim of high K^{trans} region.

Adventitial measurements were calculated by averaging all the pixels along the wall boundary. Plaque measurements were calculated by averaging all the pixels between the wall and lumen boundary. The PK parameters of each plaque were calculated as the mean value across the slices. This method has demonstrated high inter rater reproducibility[17]. DCE-MR image analysis was performed by AU and US (with more than 10yrs of image analysis experience).

Statistical Analysis

Continuous variables are presented as median (interquartile range). Data normality was assessed by Shapiro-Wilk's test. The Man-Whitney U test was used to compare the PK parameters for both the groups. Unpaired t-tests were used for comparison of continuous variables with normal distribution. Mann-Whitney was used for variables with non-normal distribution. Chi-square test was used for comparison of categorical variables. P values less than 0.05 were defined as statistically significant.

Results

All patients underwent DCE-MR imaging of vertebral arteries successfully. Patient demographics are presented in Table I. The two clinical groups of symptomatic and asymptomatic patients had comparable demographics and comorbidities (Table II). Total imaging time was ~30 minutes. Vertebral stenosis was identified in 40 arteries with a mean luminal stenosis of 55±2% and mean vessel wall area 25.46 ± 8.48mm^2. The PK values were used for statistical analysis.

Adventitial K^{trans} and plaque K^{trans} in patients with concomitant symptomatic carotid artery disease (Group 1) were significantly higher compared to the asymptomatic carotid artery disease cohort [0.08 ± 0.01min^{-1}, 0.07 ± 0.01min^{-1} versus 0.06± 0.01 min^{-1}, 0.06 ± 0.01 min^{-1} respectively, $p<0.05$] (Table III, Figure III). V_p was comparable for the two groups with no significant difference (Table III adventitial v_p 10.80 ± 6.04% vs 9.88 ± 4.95, p= 0.26; plaque v_p 8.87 ± 6.61 vs 12.14 ± 6.05%, p= 0.28, respectively). The parameter Vp represents the fraction of total volume that is plasma and has shown correlation with histologically determined microvessel density[4], however k^{trans} is the more reliable parameter to describe the imaging kinetics as it represents not only the microvessel density but also the factors like

macrophage density that influence microvessel permeability[5]. Good correlation was present among the two image analysts i.e intra-class correlation coefficient = 0.78 (Figure IV).

The images in Fig III are from a symptomatic patient with moderate stenosis in the right vertebral artery. Surface irregularity can be observed in both pre- and post-contrast T1w images. The VVI shows regions of high K^{trans} in the adventitia and relatively low K^{trans} within the plaque.

Discussion

Stroke remains one of the leading cause of cerebrovascular-related mortality and long-term disability worldwide posing a considerable burden to the global economy. Vertebral artery atherosclerosis is a significant cause of posterior circulation ischemic stroke[20]. The course of vertebrobasilar disease depends on the severity of stenosis and adequacy of collateral circulation[21]. Extracranial vertebral artery is the most common location of atherosclerotic disease within posterior circulation[8, 9, 22, 23]. Proximal vertebral artery can cause sudden-onset strokes or TIAs most commonly presenting as dizziness during TIAs which may be complemented by other signs such as vertigo, diplopia, oscillopia, hemiparesis, weakness of both legs, and numbness. Distal vertebral artery stenosis seems to carry a higher risk for brain stem infarction which is commonly fatal[24]. Disease usually follows a long course and patient may remain asymptomatic or eventually become symptomatic with more lethal consequences such as cerebral or brainstem ischemia leading to severe morbidity or death [25, 26]

Besides luminal stenosis, vertebral atheroma morphology and underlying functional activity such as inflammation seem to determine the severity of vertebral atherosclerosis. DCE MR imaging is a promising non-invasive method to identify plaque neovascularization and indirectly the plaque inflammation in various vascular territories. The average K^{trans} within the adventitia and plaque, as a quantitative measure of neovessel permeability and degree of

neovascularization has demonstrated significant correlation with histopathological determined macrophage infiltration, microvessel density and permeability[5] and increased plaque instability[27]. This has been validated in previous studies with histopathological analysis[5].

The aim of this study was to assess the feasibility of DCE-MR imaging in evaluation of neovascularization in vertebral arterial wall and to explore the difference in the degree of MR defined neovascularization in vertebral territory in patients with concomitant symptomatic or asymptomatic carotid artery disease. DCE MR imaging has been previously used successfully for assessing neovascularisation in carotid and vertebral arteries[4, 5, 28]. The primary findings of this study were as follows:

1. 3D DCE MR Imaging is a feasible technique to assess neovascularization in vertebral territory.
2. Patients with completely asymptomatic vertebral artery disease and symptomatic carotid artery disease (Group 1) had more neovessel formation in vertebral territory compared to the completely asymptomatic cohort as demonstrated by high adventitia K^{trans} in contrast to the plaque K^{trans}.
3. Completely asymptomatic individuals (Group 2) demonstrated low adventitia K^{trans} and plaque K^{trans} which indicates decreased neovascularization in this patient cohort.

These findings are consistent with the hypothesis that one inflamed symptomatic vascular bed (carotid) is likely to increase the risk of other arterial vessels to become inflamed (vertebral territory).

Previously our group has reported the use of USPIO-enhanced carotid MR imaging with a (ultrasmall superparamagnetic particle of iron oxide), to highlight the systemic nature of atherosclerosis. In the series of comparative studies, it was observed that the carotid plaques

of truly asymptomatic patients have lesser degree of USPIO identified plaque inflammation than the carotid plaques on the contralateral side to the symptomatic carotid artery[29]. Similarly, it was seen in patients with truly asymptomatic carotid artery disease but with active coronary artery disease to have more inflammation in carotid plaques, compared with those in truly asymptomatic patients with no coronary artery disease[30]. The degree of plaque inflammation was observed to have no correlation with severity of carotid artery luminal stenosis[31].

Recently several studies were conducted to investigate the association between DCE MRI parameters, plaque inflammation and presence of plaque haemorrhage (PH)[32, 33]. Also, varying degree of correlation was observed between DCE MRI parameters and positron emission tomography defined plaque inflammation in various clinical studies[34-36]. DCE MRI has also been used to assess the effect of various pharmacological interventions. Significant reduction in k^{trans} was observed in one-year follow-up in patients with known carotid artery disease on intensive lipid lowering therapy. This reduction in k^{trans} is indicative of the reduction in the extent and permeability of atherosclerotic plaque neovasculature[37].

The results from our study suggested that DCE-MRI may be a useful imaging tool for assessment of plaque neovascularization in vertebral artery disease and a reliable marker to assess the systemic nature of atherosclerosis. This might be used to evaluate the plaque microvasculature changes over time in different patient cohorts with significant risk factors and may be implicated to assess the therapeutic effects of various pharmacological interventions in this vascular territory.

Study Limitations

A relative limitation of this study is the lack of histological validation. Vertebral artery endarterectomy is however only rarely performed[38], with best medical therapy and angioplasty[39] as preferred treatments for VA disease. Another limitation is that vertebral vessels are small, and it is difficult to delineate the plaque components hence the correlation between the individual plaque components and kinetic values could not be demonstrated.

Conclusions:

In conclusion, this study established a comprehensive approach for analysis of DCE-MRI of vertebral atherosclerotic plaque by utilising kinetic modeling illustrated by coloured vasa vasorum images. Future studies with greater sample size are warranted to evaluate the predictive potential of VA DCE-MR imaging based plaque neovascularization for plaque progression and association with recurrent cerebrovascular events.

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Disclosures

None

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Figure Legends:

Figure I: Axial images on T_1 w DANTE CUBE. Stenosis of left vertebral artery can be visualized. The TOF (Time of Flight) shows almost no blood flow through the Left vertebral artery indicating the stenosis on L side as compared to the R side. The magnified view shows the lumen (L) and plaque (P).

Figure II: Processed three- dimensional data showing stenosis in left vertebral artery (A) Manual delineation of lumen and vessel wall on T_1w images (B) ROIs co –registered on VVIs by manual adjustment (C) Adventitial and plaque pharmacokinetic measurements calculated pixel wise along their respective boundaries(D) Represents the mean signal intensity time course within the lumen(red) and adventitia (green**).**

Figure III: Shows the oblique and axial reformat of pre and post contrast T_1w and Vasa Vasorum images(VVI) (A) Pre contrast T_1 weighted image showing left vertebral artery stenosis and (B)shows post contrast (gadolinium) T_1w enhancement(C) indicates the K^{trans} (green channel) in VVI ranges from 0 to 1min^{-1} Vp (red channel) ranges from 0-100%.

Figure IV: Comparison of pharmacokinetics parameters in Group 1 (patients with symptomatic carotid artery disease) and Group 2 (patients with asymptomatic carotid artery disease) (A) adventitial K^{trans} (B) plaque K^{trans} (C) intra class correlation.

Table Legends:

Table I: Study Population Demographics

Table II: Comparison of demographics and continuous variables of patients with symptomatic and asymptomatic carotid artery disease

Table III: Mean values of pharmacokinetic and morphological measurements