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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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

magnetic resonance angiography (CE-MRA) of the cervical segment of both VAs. Acquisition time was 6 minutes and 23 seconds to obtain a mask image and 30 temporally interpolated phases with a temporal resolution of 10.6 seconds. Coincident with the third phase, a bolus of .1 mmol/kg Gd-DPTA (Gadovist, Bayer Schering, Berlin, Germany) was administered intravenously with an MR-compatible power syringe at a flow rate of 3 mL/s followed by a 20-mL saline flush. The CE-MRA data were obtained by subtracting the baseline scan from the multiphase acquisition.

In addition, the following sequences were used for morphometric assessment of VA wall: pre- and postcontrast 3-D T_1w delays alternating with nutation for tailored excitation (DANTE)-prepared fast spin echo[14] (variable flip angle; TE/TR, 16.9/540; field of view, $140 \times 140 \times 67$; matrix, $224 \times 224 \times 48$; acquisition time, 2×6 minutes and 26 seconds) (DANTE-black blood), 3-D time of flight (TOF) (flip angle, 20°; TE/TR, 2.2/5.9 ms; field of view, $140 \times 140 \times 64$ mm; matrix, $256 \times 256 \times 32$; acquisition time, 1 minute and 35 seconds).

Image Analysis

The T_1w and DCE images were reformatted into the axial plane with a .7-mm slice thickness using an Advantage Workstation (version 4.6, GE Healthcare) (Fig 1). For each patient, VAs of both sides were analyzed. On average 15-20 axial slices per side per patient were analyzed. Inner- and outer-wall contours were drawn manually, thereby determining the vessel wall region of interest at each slice according to the multicontrast images, using the OsiriX DICOM viewer (version 5.5.2, PixmeoSari, Geneva, Switzerland) (shown in Fig 1). Vessel wall and lumen boundaries were mainly based on precontrast T_1w images. The subtracted CE-MRA image at the fifth phase, which has highest contrast of the VA, was used for analysis. Vessel wall area was calculated as a difference between lumen area and total vessel wall area using 3-D DANTE CUBE sequence. Luminal stenosis was measured for each plaque using European Carotid Surgery Trial criteria.[15] Of the retrieved images, 70% were of sufficient quality according to the set 5-point scale (1 = poor, 5 = excellent), which were to be used for quantitative analysis. The image quality (IQ) was rated by previously published 5-point scale.[16] Images with IQ greater than 3 were included for morphological analysis, whereas images with IQ greater than 4 were included for quantitative analysis. Four patients with IQ score less than 3 were excluded.

Pharmacokinetic (PK) Modeling

Images from the acquired data were processed using the vasa vasorum imaging (VVI) tool of the University of Washington (Seattle) .[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 2-compartment Patlak model[19] is then used to generate a parametric map known as the "vasa vasorum image (VVI)" showing partial plasma volume

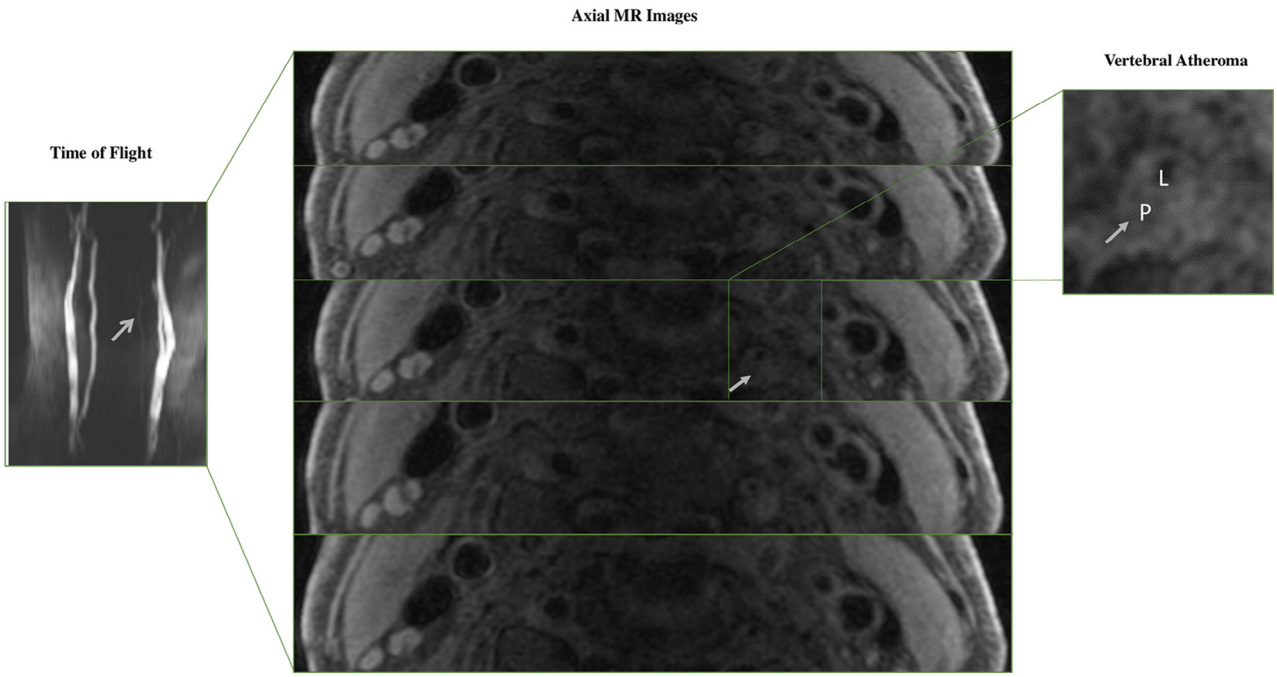

Figure 1. *Axial images on T_1w DANTE CUBE. Stenosis of left vertebral artery can be visualized. The time of flight (TOF) shows almost no blood flow through the left vertebral artery, indicating the stenosis on the left side compared with the right side. The magnified view shows the lumen (L) and plaque (P).*

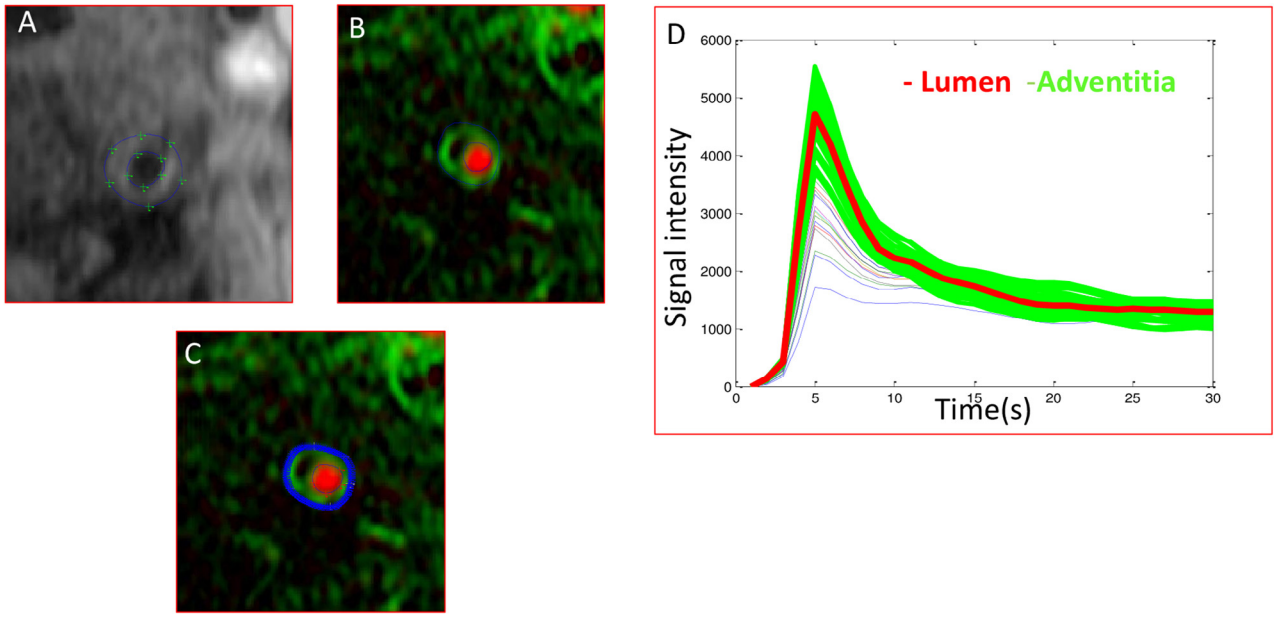

Figure 2. *Processed 3-dimensional data showing stenosis in left vertebral artery. (A) Manual delineation of lumen and vessel wall on T_1w images. (B) ROIs co-registered on VVIs by manual adjustment. (C) Adventitial and plaque pharmacokinetic measurements calculated pixel wise along their respective boundaries. (D) Mean signal intensity time course within the lumen (red) and adventitia (green) are represented. Abbreviations: ROI, region of interest; VVI, vasa vasorum imaging. (Color version of figure is available online.)*

(v_p) in shades of red and transfer constant (K^{trans}) in shades of green (Fig 2). The relationship between blood and tissue signal concentration is modeled as follows:

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

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-MRI analysis was performed by A.U. and U.S. (with more than 10 years of image analysis experience).

Statistical Analysis

Continuous variables are presented as median (interquartile range). Data normality was assessed by Shapiro-Wilk's test. The Mann–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 .05 were defined as statistically significant.

Results

All patients underwent DCE-MRI of VAs successfully. Patient demographics are presented in Table 1. The 2 clinical groups of symptomatic and asymptomatic patients had comparable demographics and comorbidities (Table 2). 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

Table 1. *Study population demographics*

Characteristics	n (%)
Number of patients	20
Median age (years) [IQ]	73 [65.5-77.5]
Male	13 (65%)
Hyperlipidemia	17 (85%)
Hypertension	14 (70%)
Diabetes mellitus	7 (35%)
Peripheral vessel disease	1 (5%)
Ischemic heart disease	5 (25%)
Previous carotid endarterectomy	10 (50%)
Statin	18 (90%)
Clopidogrel	14 (70%)
Aspirin	16 (80%)

Abbreviation: IQ, interquartiles.

Table 2. *Comparison of demographics and continuous variables of patients with symptomatic and asymptomatic carotid artery disease*

	Symptomatic CAD (n = 10)	Asymptomatic CAD (n = 10)	*P* value (2-tailed)
Age (y)	69.5 (67.2-74.7)	77 (63-80)	.48*
Vascular events (TIA/stroke)	10 (100%)	5 (50%)	.04*
Ischemic heart disease	1 (10%)	4 (40%)	.30*
CEA	8 (80%)	2 (20%)	.03*
HTN	7 (70%)	7 (70%	1.00*
Hyperlipidemia	9 (90%)	8 (80%)	.53*
Statin	9 (90%)	9 (90%)	1.00*
Clopidogrel	8 (80%)	7 (70%)	.60*
Aspirin	9 (90%)	6 (60%)	.12*
ACE inhibitor	1 (10%)	4 (40%)	.12*
HDL (mmol/L)	1.37 ± .26	1.05 ± .11	.007†
LDL (mmol/L)	2.60 ± .43	2.61 ± .88	.96†
Chol/HDL Ratio	3.5 ± .84	4.25 ± .81	.045†
TG (mmol/L)	1.5 ± .35	1.76 ± .37	.11†
CRP (mg/L)	5.07 ± 1.38	5.4 ± 1.87	.82†

Abbreviations: ACE, angiotensin-converting enzyme; CAD, coronary artery disease; CEA, carotid endarterectomy; Chol, cholesterol; CRP, C-reactive protein; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; TG, triglycerides; TIA, transient ischemic attack.

*Chi-square.

†Mann–Whitney test.

25.46 ± 8.48 mm^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 with the asymptomatic carotid artery disease cohort [.08 ± .01 min^{-1}, .07 ± .01 min^{-1} versus .06 ± .01 min^{-1}, .06 ± .01 min^{-1}, respectively, $P < .05$] (Table 3, Fig 3). The v_p was comparable for the 2 groups with no significant difference (Table 3; adventitial v_p 10.80% ± 6.04% versus 9.88 ± 4.95, $P = .26$; plaque v_p 8.87 ± 6.61 versus 12.14% ± 6.05%, respectively, $P = .28$). The parameter v_p 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 such as macrophage density that influence microvessel permeability.[5] Good correlation was present between two image analysts (i.e., intraclass correlation coefficient = .78; Fig 4).

Table 3. *Mean values of pharmacokinetic and morphological measurements*

	Group 1 (mean)	Group 2 (mean)	*P* value
K^{trans} adventitia (min^{-1})	.08 ± .01	.06 ± .01	.004*
K^{trans} plaque (min^{-1})	.07 ± .01	.06 ± .01	.03*
v_p_adventitia (%)	10.80 ± 6.04	9.88 ± 4.95	.26*
v_p (%)	8.87 ± 6.61	12.14 ± 6.05	.28*
Mean plaque area cm^2	.27 ± .13	.23 ± .06	.45*
Mean luminal stenosis	54.4 ± 4.66	52.7 ± 5.74	.28*

*Mann–Whitney test.

The images in Figure 3 are from a symptomatic patient with moderate stenosis in the right VA. Surface irregularity can be observed in both pre- and postcontrast T_1w 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 causes of cerebrovascular-related mortality and long-term disability worldwide, posing a considerable burden to the global economy. VA 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 VA is the most common location of atherosclerotic disease within posterior circulation.[8,9,22,23] Proximal VA can cause sudden-onset strokes or TIAs most commonly presenting as dizziness, which may be complemented by other signs such as vertigo, diplopia, oscillopia, hemiparesis, weakness of both legs, and numbness. Distal VA stenosis seems to carry a higher risk for brain stem infarction,

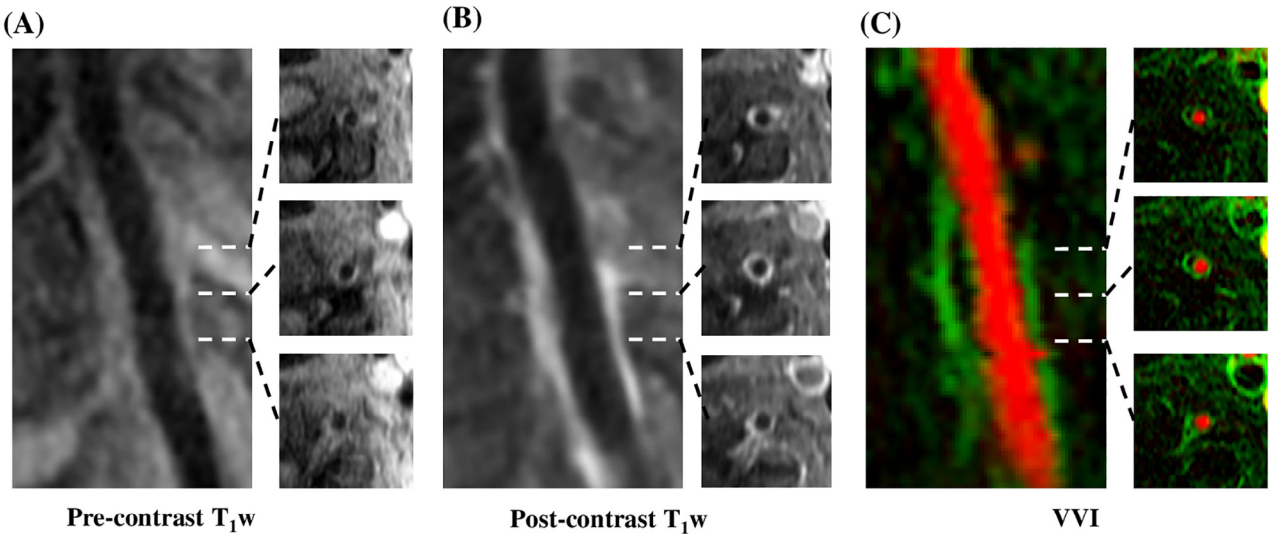

Figure 3. *Oblique and axial reformat of pre- and postcontrast T_1w and vasa vasorum images are shown. (A) Precontrast T_1w image shows left vertebral artery stenosis and (B) shows postcontrast (gadolinium) T_1w enhancement. Panel (C) indicates the K^{trans} (green channel) in VVI ranges from 0 to 1 min^{-1} and v_p (red channel) ranges from 0% to 100%. (Color version of figure is available online.)*

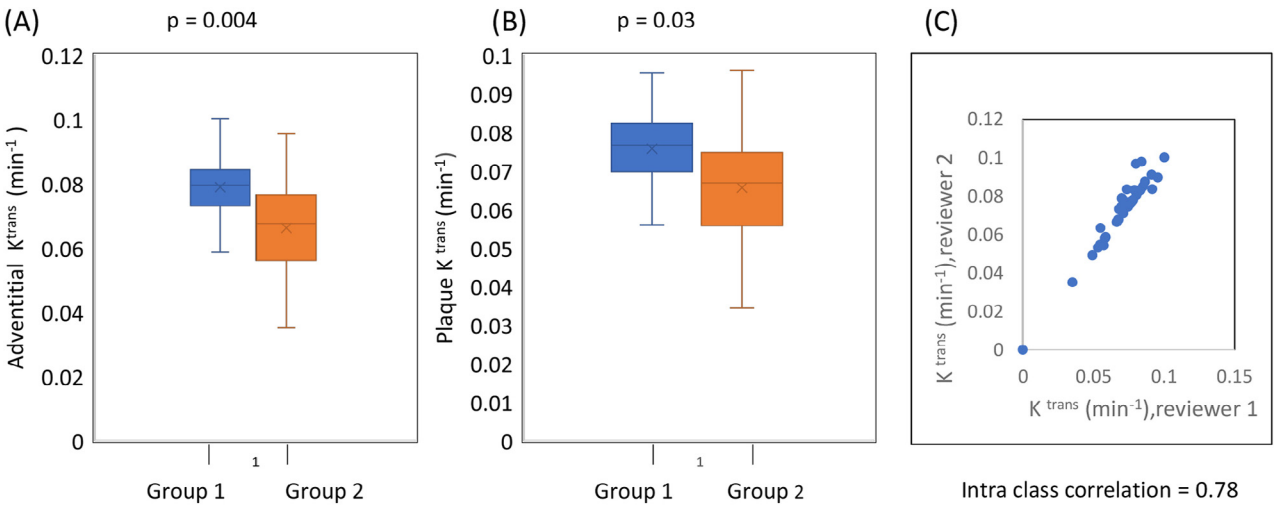

Figure 4. *Comparison of pharmacokinetic parameters in group 1 (patients with symptomatic carotid artery disease) and group 2 (patients with asymptomatic carotid artery disease): (A) adventitial K^{trans}, (B) plaque K^{trans}, and (C) intraclass correlation.*

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 brain stem 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-MRI is a promising noninvasive 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 histopathologically 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-MRI 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-MRI has been previously used successfully for assessing neovascularization in carotid

and VAs.[4,5,28] The primary findings of this study were as follows:

1. 3-D DCE-MRI is a feasible technique to assess neovascularization in vertebral territory.
2. Patients with completely asymptomatic VA disease and symptomatic carotid artery disease (group 1) had more neovessel formation in vertebral territory compared with 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 1 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 ultrasmall superparamagnetic particle of iron oxide (USPIO)-enhanced carotid MRI 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 1-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 VA 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. VA 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 utilizing kinetic modeling illustrated by colored vasa vasorum images. Future studies with greater sample size are warranted to evaluate the predictive potential of VA DCE-MRI-based plaque neovascularization for plaque progression and association with recurrent cerebrovascular events.

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