In vivo assessment of adventitial vasa vasorum in patients with symptomatic carotid plaques: A dynamic contrast-enhanced MRI study.

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Introduction: Adventitial vasa vasorum (VV) proliferates and gives rise to intraplaque neovascularization during the atherogenic process.[1] Subsequently, fragile neovessels may facilitate the influx of inflammatory cells and erythrocytes.[2] Therefore, adventitial VV is thought to be a primary source of intraplaque hemorrhage (IPH) and may be a surrogate marker for plaque destabilization. Recently, dynamic contrast-enhanced MRI (DCE-MRI) is emerging as a promising tool to characterize adventitial VV noninvasively in humans.[3,4] The aims of this study were: 1) to test the hypothesis that adventitial VV as assessed by DCE-MRI is associated with IPH; 2) to evaluate the potential of adventitial VV quantification in discriminating symptomatic from asymptomatic plaques in the carotid artery.

Methods: *Patients:* A total of 27 symptomatic patients (22 men; 69±10 years) were referred to carotid MRI after informed consent with the following inclusion criteria: 1) transient ischemic attack or ischemic stroke in the distribution of the index carotid artery within the past 6 months (time interval: 23±37 days); 2) ipsilateral carotid plaque confirmed by ultrasound; 3) no atrial fibrillation or intracranial carotid stenosis. *MRI protocol:* Patients were scanned using a 3T scanner (Achieva, Philips, the Netherlands) and eight-channel phased-array surface coils. A standardized multi-contrast MRI protocol was used for plaque characterization (3D time-of-flight [TOF], T1, proton density, T2, MP-RAGE [magnetization-prepared rapid acquisition gradient-echo]).[5] A 2D spoiled gradient recalled echo sequence was used for DCE-MRI with the following parameters: TR/TE = 115/4.6 ms, flip = 50°, field of view = 16X16 cm, matrix = 256X253, thickness = 2 mm, no inter-slice gap. DCE-MRI images were simultaneously acquired at 12 slices, and at 12 time points separated by a repetition interval of 14 s. Coincident with the second image in the sequence, 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist, Bayer, Germany) was injected at a rate of 2 ml/s by a power injector. *Image analysis:* Multiple weightings were used to determine the presence of IPH for each artery. A hyper-intense signal in wall area on MP-RAGE indicated the presence of IPH, which was corroborated by TOF/T1-weighted images.[6] DCE-MRI analysis was performed using a kinetic modeling approach.[4] For each slice, images were automatically processed to produce a color-coded parametric map that shows the transfer constant (K^{trans}) in green and plasma volume (v_p) in red (Figure 1). The lumen boundary was placed around the red lumen with high v_p. The outer wall boundary was placed to coincide with the rim of high K^{trans} defining the adventitia. Adventitial K^{trans} was computed by averaging all pixels within the 1-pixel thick layer just within the outer wall boundary. Maximum and mean adventitial K^{trans} values across all slices were then calculated for each artery. *Statistical analysis:* Data were presented as mean±standard deviation or count (percentage). McNemar's test was used to compare the prevalence of IPH between symptomatic and asymptomatic sides. A linear mixed model was used to compare adventitial K^{trans} between IPH and non-IPH arteries. Paired and unpaired t-tests were used as appropriate to compare adventitial K^{trans} between the two sides.

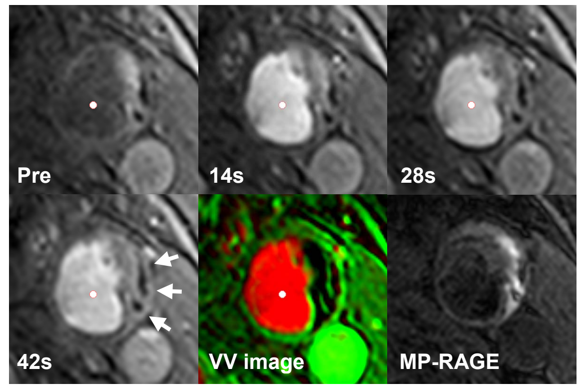

Figure 1. A representative case with IPH. Upper panel and the left image in lower panel show the dynamic enhancement of adventitia (white arrows). The lumen appears red in the parametric image whereas the adventitia appears as a green rim (middle image in lower panel). The right image in lower panel shows IPH as a bright area on MP-RAGE. IPH = intraplaque hemorrhage; MP-RAGE = magnetization-prepared rapid acquisition gradient-echo; Pre = pre-contrast; s = seconds; VV = vasa vasorum.

Results: *IPH prevalence:* IPH was present in 12 (44.4%) of the symptomatic arteries compared with 4 (14.8%) of the asymptomatic arteries (p=0.027). *Adventitial K^{trans} and IPH:* Two arteries on the asymptomatic side were plaque-free and therefore excluded from DCE-MRI image analysis. Additionally, one patient with IPH on the symptomatic side had no K^{trans} measurement bilaterally due to low signal-to-noise ratio of DCE-MRI images. Of the remaining arteries, IPH arteries (n=15) showed significantly higher adventitial K^{trans} compared to non-IPH ones (n=35) (maximum: 0.142±0.042 vs. 0.112±0.029, p=0.004; mean: 0.103±0.034 vs. 0.083±0.020, p=0.015). *Adventitial K^{trans} and symptom:* Overall, adventitial K^{trans} was higher on the symptomatic side (Table 1). Subgroup analysis showed that IPH arteries tended to have higher K^{trans} regardless of symptom status, whereas non-IPH arteries on the symptomatic side had higher maximum adventitial K^{trans} compared to those on the asymptomatic side (Table 1).

Table 1. Comparison of artery-wise adventitial K^{trans} between the symptomatic and asymptomatic sides.

	Patients with bilateral K^{trans}			IPH arteries with K^{trans}			Non-IPH arteries with K^{trans}		
	n	Maximum	Mean	n	Maximum	Mean	n	Maximum	Mean
Symptomatic	24	0.134±0.038	0.097±0.030	11	0.146±0.047	0.108±0.036	15	0.125±0.027	0.088±0.021
Asymptomatic	24	0.107±0.027	0.082±0.021	4	0.131±0.023	0.089±0.029	20	0.102±0.027	0.080±0.020
p value		**0.001***	**0.036***		0.562†	0.373†		**0.013†**	0.291†

* Paired t-test. † Unpaired t-test.

Discussion: This study in symptomatic patients demonstrated a close association between adventitial VV and IPH. In fact, IPH arteries appeared to have high adventitial K^{trans} regardless of their symptom status. It thus supports the notion that leaky neovessels originating from adventitial VV may be the primary source of IPH.[2] Alternatively, the high adventitial K^{trans} associated with IPH arteries may be a response to elevated inflammatory stress once IPH occurs. A prospective study is desired to further elucidate their relationship. Although both IPH and adventitial K^{trans} were found to discriminate symptomatic from asymptomatic plaques, symptomatic non-IPH arteries showed higher maximum adventitial K^{trans} compared to asymptomatic non-IPH ones. Adventitial K^{trans} measured by DCE-MRI may provide complementary information in individual risk stratification. Additionally, maximum adventitial K^{trans} appeared to be superior to mean values in discriminating IPH from non-IPH arteries or symptomatic from asymptomatic plaques. The heterogeneous distribution of adventitial K^{trans} and its implications warrants further studies.

Conclusion: Adventitial VV assessed by DCE-MRI in vivo was associated with IPH and clinical symptom status. DCE-MRI provides a noninvasive way to characterize adventitial VV in patients and may be useful in studying plaque progression or individual risk stratification, but further examination in prospective studies is needed.

References: 1. Moreno PR, et al. *Circulation,* 2006; 2. Virmani R, et al. *ATVB*, 2005; 3. Aoki S, et al. *JMRI*, 1999; 4. Kerwin WS, et al. *MRM*, 2008; 5. Li FY, et al. *JMRI*, 2009; 6. Ota H, et al. *Radiology*, 2010.