

SEX DIFFERENCES OF HIGH-RISK CAROTID ATHEROSCLEROTIC PLAQUE IN ASYMPTOMATIC PATIENTS WITH VARYING LEVELS OF STENOSIS -IN VIVO 3.0T MRI STUDY

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Introduction: A prior study of carotid endarterectomy (CEA) specimens demonstrated sex differences in plaque morphology, indicating that men had more unstable plaque compared to women¹. However, such histological studies are based on a limited spectrum of carotid atherosclerosis in patients with severe luminal stenosis. Little is known whether the similar sex differences exist across the entire spectrum of plaque development. Non-invasive in vivo carotid MR imaging can provide detailed data on vessel wall morphology and plaque characteristics from a much broader range of patients^{2,3}.

Purpose: To evaluate prevalence of complicated, high-risk carotid plaque characteristics in both men and women with a broad range of carotid artery stenosis.

Materials and Methods: One-hundred-thirty-nine patients (52% men) with $\geq 50\%$ asymptomatic stenosis of at least one carotid artery as measured by screening duplex ultrasound were included. Information of sex, age, hyperlipidemia, hypertension, history of coronary artery disease, peripheral vascular disease, diabetes mellitus, current statin use and smoking were collected. All subjects underwent a bilateral carotid MR imaging using a GE 3T scanner with a dedicated four-channel carotid coil. Multi-contrast carotid MRI protocol included 5 different weightings: 3D time-of-flight, pre-contrast T1-weighted, T2-weighted, 3D inversion recovery fast spoiled gradient recalled (3D IR FSPGR)⁴ and GdDTPA contrast-enhanced T1-weighted sequences. Images were acquired in the axial plane and centered to include bilateral carotid bifurcations. All the images were obtained with a field of view of 14 to 16 cm, matrix size of 256x256, slice thickness of 1 to 2 mm. After intravenous bolus contrast injection, a very high (0.28 mm³) resolution coronal elliptical-centric carotid CE MR angiogram was also performed. Two experienced radiologists interpreted each carotid image through a consensus opinion process using published criteria previously validated by histology. The reviewers were blinded to subjects' clinical information and image review results of the contralateral carotid. An Image quality (IQ) score was rated per artery on a 4-point scale (1=poor, 4=excellent). Arteries with an average of IQ of 1, prior CEA or occluded arteries were excluded from image review. The extracranial carotid bifurcation level was used as a landmark for matching the five different weightings. For each artery, the presence of complicated American Heart Association type VI (AHA-type VI, plaques with luminal surface defect, hemorrhage/thrombus, or calcified nodules)³ was documented. In addition, the presence of individual plaque characteristics: lipid-rich necrotic core, thin/ruptured fibrous cap, intraplaque hemorrhage and calcification were documented. Lastly, two radiologists, blinded to clinical information and results of plaque imaging, evaluated the degree of diameter stenosis as measured by CE-MR angiogram based on NASCET criteria, using a consensus approach.

The prevalence of AHA-type VI and level of stenosis was compared between male and female patients. Univariate logistic models (for categorical data) and linear regression models (for continuous data) were first undertaken to identify sex differences in demographic variables. These factors were considered as potential confounders in the multivariate models if the univariate $p < 0.20$. Multivariable logistic regression models were fit to determine the association of sex (male vs. female) with binary plaque features (i.e., presence of AHA type VI lesion, lipid-rich/necrotic core, thin/ruptured fibrous cap, intraplaque hemorrhage and calcification), while controlling for the level of stenosis. The logistic regression models were fit using generalized estimating equations (GEE) with exchangeable correlation structure in order to adjust for the correlation of the two sets of measures per patient (i.e., bilateral carotids). Variables were selected into the final multivariate model using stepwise forward method ($p < 0.10$ for entry). Final model results generated adjusted odds ratios (aORs) with 95% confidence intervals. Degree of stenosis was included in all models regardless of significance.

Results: Forty-eight (17%) of the total 238 arteries were excluded from image analysis due to poor image quality (n=12), prior CEA (n=20) or occlusion (n=16). Accordingly, 230 arteries (117 men, 113 women) in 132 patients (67 men, 65 women) were included for the analysis. Out of 132 patients, 98 provided bilateral carotids for the analysis. History of coronary artery disease (OR=2.4, 95%CI, 1.2, 4.9, $p=0.02$) and higher use of statins (86% vs. 75%, $p=0.11$) were more common in men, while there was a lower incidence of hyperlipidemia (male vs. female, 71% vs. 85%, $p=0.11$) in men compared to women. Results of the final multivariable logistic regression models are shown in Table 1. Sex and MRA degree of stenosis were independently and significantly associated with presence of AHA type VI, lipid-rich necrotic core, thin/ruptured fibrous cap and intraplaque hemorrhage. There was no significant association between sex and calcification and no other variables we entered in the final models. Figure 1 demonstrates a trend towards an increase in the prevalence of AHA-type VI with increasing levels of categorized carotid stenosis (from 0-29% to 80-99%), as well as a higher prevalence in men compared to women across all stenosis categories.

Conclusions: In this population, male gender was significantly associated with complicated AHA type VI plaque as well as presence of

thin/ruptured fibrous cap, lipid-rich necrotic core and intraplaque hemorrhage compared with females while controlling for the level of stenosis. Increasing MRA stenosis was also associated with these high-risk plaque features. The present results indicate that the development of atherosclerosis appears different between men and women. These results also indicate possible importance of sex-based management for patients with asymptomatic carotid atherosclerosis.

References: 1. Hellings WE, et al. *J Vasc Surg.* 2007;45:289-96. 2. Yuan et al. *NMR Biomed.* 2006;19:636-54. 3. Saam et al. *J Am Coll Cardiol.* 2008; 51:1014-21. 4. Zhu D et al. *Magn Reson Imaging.* 2008;26:1360-6. 5. Yarnykh et al. *Magn Reson Med* 2002;48:899-905.

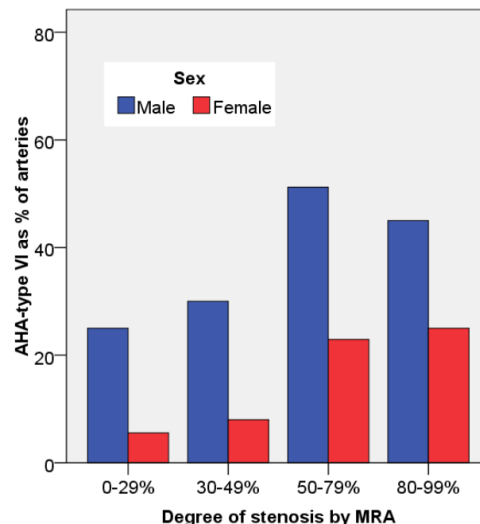


Table 1. Associations among sex, MRA degree of stenosis and plaque characteristics.

	Male*			MRA stenosis†		
	aOR	95% CI	p	aOR	95% CI	p
AHA type VI,	4.1	2.1-8.0	<0.001	1.2	1.1-1.3	0.004
Lipid-rich/necrotic core	3.6	1.9-6.8	<0.001	1.2	1.1-1.3	<0.001
Thin/ruptured fibrous cap	4.9	2.4-10.1	<0.001	1.3	1.1-1.5	<0.001
Intraplaque hemorrhage	2.9	1.4-6.1	0.003	1.2	1.0-1.3	0.011
Calcification	1.2	0.6-2.6	0.579	1.2	1.1-1.5	0.005

*aOR for male vs. female; †aOR for 10% increase, ORs were adjusted for subjects' demographic data with $p < 0.20$ in univariate models.