MRI determined carotid artery flow velocities and wall shear stress in a mouse model of vulnerable and stable atherosclerotic plaque

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Introduction: We report here on the pre-clinical MRI characterization of an apoE-/- mouse model of stable and vulnerable carotid artery atherosclerotic plaques, which were induced by a tapered restriction (cast) around the artery. Specific focus was on the quantification of flow velocities and wall shear stress (WSS), which are considered key players in the development of the plaque phenotype. Specifically, lowered shear stress was related to a vulnerable plaque phenotype, while an oscillatory nature of the wall shear stress was associated with a stable plaque phenotype, as evidenced by extensive histological analysis.

Methods: Experiments were performed on 6 female apoE-/- mice on Western type diet. A tapered cast was surgically placed around the right carotid artery to induce a vulnerable and stable plaque phenotype upstream and downstream from the cast, respectively [1]. In vivo MRI was performed at 9.4T. TOF MRA was done with a 3D gradient echo sequence with: TR=15 ms, TE=2.5 ms, α=20°, FOV=2.56^3 cm^3, matrix=256^3, NA=2, scan time=18 min. T1w and T2w imaging was performed using an ECG-triggered black blood spin echo sequence. Parameters for T1w imaging were: TR=800 ms, TE=7.5 ms, FOV=2.56^2 cm^2, matrix=256^2, slice thickness=0.5 mm, NA=2, scan time=8 min, and for T2w imaging: TR=2000 ms, TE=20 ms, NA=2, scan time=20 min. Phase-contrast velocity imaging was done using an ECG-triggered gradient echo sequence with flow encoding perpendicular to the imaging slice, with: TR=12 ms, TE=5 ms, α=30°, FOV=2.56^2 cm^2, matrix=384^2, slice thickness=0.5 mm, NA=6, V_{enc}=100 cm/s, scan time=18 min. The sequence was triggered by the QRS-complex and repeated 3 times with delays of 1, 5, and 9 ms, resulting in 27 cardiac frames. Four ROIs were drawn to select the lumen of the left and right carotid arteries in the downstream and upstream images. For determination of WSS=μ·dv/dr flow profiles at the wall were fitted with a quadratic polynomial (assumed blood viscosity μ=10 mPa·s).

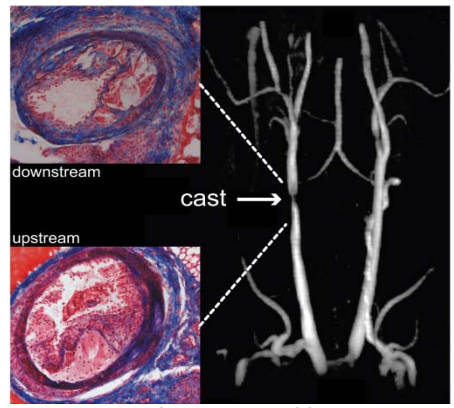


Figure 1: MIP of the 3D time of flight MRA. The arrow indicates the position of the tapered cast. The insets show masson-trichrome stained sections of the plaques.

Results: Fig. **1** displays a MIP of a time of flight angiography measurement of the neck area of a mouse and masson-trichrome stained histological sections, confirming the presence of vulnerable and stable plaque phenotypes, upstream and downstream, respectively. The presence of high blood signal intensity downstream to the cast extending beyond the carotid bifurcation and further, confirms that the vessel is still patent. The tapered shape of the cast can be appreciated in the image, which confirms correct placement of the cast around the right carotid artery. The average diameters of the carotid artery lumen at the 4 positions, i.e. right carotid upstream, right carotid downstream, left carotid upstream, and left carotid downstream, were 0.57±0.12mm, 0.41±0.17mm, 0.54±0.11mm, and 0.49±0.08mm, respectively. Flow measurements were analyzed in the left and right. Fig. **2A** shows a T1w image at the upstream location, with color-coded flow velocities in the left and right carotid arteries. The panels in Fig. **2B** show the flow profiles along the red lines numbered 1 to 4. The profiles display a quadratic shape, indicative for laminar flow, except for the right carotid artery at downstream position, where the apparent flow is low and irregular. Figs. **3A,B** show the flow velocities as function of time through the cardiac cycle. WSS at maximum flow velocity is plotted in Fig. **3C**. WSS at the 3 locations, i.e. right carotid upstream, left carotid upstream, and left carotid downstream, were 11.2±5.2Pa, 17.5±7.5Pa, and 24.5±10.9Pa, respectively. WSS in the right carotid artery downstream position could not be determined as the flow profile displayed an irregular non laminar flow profile, which is consistent with the proposed oscillatory nature of the flow at this location [1].

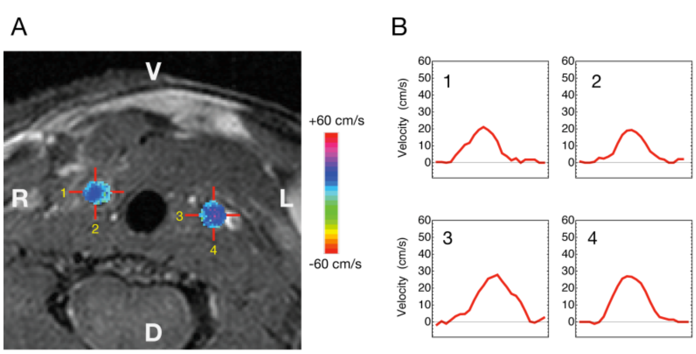
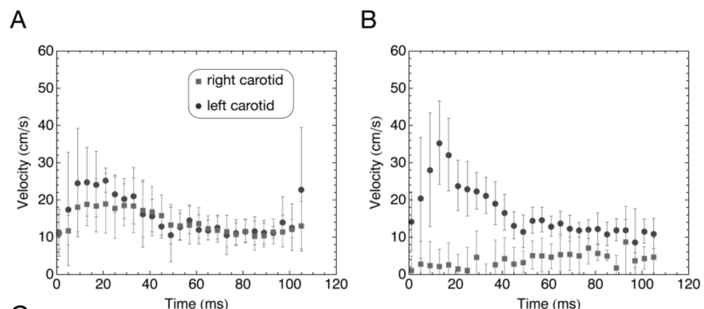


Figure 2: **A)** T1-weighted images with color-coded velocities at maximum flow in the left and right carotid arteries upstream to the cast. **B)** Flow profiles along the red lines in A, indicated by 1, 2, 3 and 4.



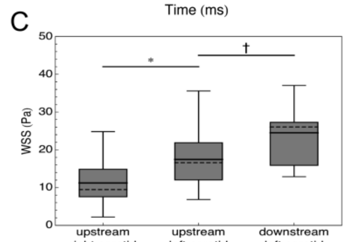


Figure 3: Flow velocities as function of time in the cardiac cycle. **A)** Upstream to the cast. **B)** Downstream to the cast. **C)** Wall shear stress. The solid line represents the mean; the dashed line the median. *,† = significantly different ($p < 0.05$).

Conclusions: The apoE-/- mouse with tapered cast represents an extremely attractive model of atherosclerosis as it allows for studying both stable and vulnerable plaque phenotypes within one animal and within a single vascular segment. This study specifically focused on anatomical MRI characterization of the model and on quantification of flow velocities and wall shear stress, related to plaque phenotype. A lowered wall shear stress was measured at the position of vulnerable plaque phenotype, whereas flow profiles were consistent with an oscillatory nature at the position of the stable plaque phenotype, which confirmed current hypothesis on the development of plaque in this mouse model.

Reference: [1] Cheng, C. et al. Circulation, 2006, 113: 2744-2753.