Hemodynamic factors associations with early atherosclerotic changes at the carotid bifurcation

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***Abstract*—Here we aimed at identifying associations between local hemodynamics and imaging markers of early atherosclerosis. At the carotid bifurcation, distinct hemodynamic factors are involved at different stages of the early atherosclerotic changes (i.e., endothelial dysfunction and adventitial neovascularization *vs*. wall thickening), and may not necessarily go hand-in-hand.**

Keywords—Atherosclerosis, wall shear stress, wall thickness, contrast enhancement.

I. Introduction

AMPLE evidence supports the role of "disturbed" blood flow in the focal development of atherosclerotic plaques, in particular low and oscillatory wall shear stress (WSS). In vivo studies on the role of hemodynamic stimuli in atherosclerosis have typically used wall thickness (WT) or intima-media thickness as a measurable surrogate markers of atherosclerotic changes to the vessel wall. However, the earliest preclinical manifestations of atherosclerosis, namely endothelial cells (ECs) dysfunction and adventitial vasa vasorum neo-vascularization, appear prior to wall thickening and apparent structural changes of the vessel wall [1].

Contrast-enhanced MRI now allows for the in vivo characterization of early atherosclerotic changes, as uptake of the contrast agent into the wall is thought to be mediated by adventitial vasa vasorum and EC permeability [2]. Moreover, MRI can be used to measure WT in vivo, and provides the anatomical and functional information required for subject-specific computational quantification and classification of local hemodynamic conditions. This allows us to compare, for the first time in vivo in humans, markers of "disturbed" WSS as obtained from patient-specific computational hemodynamics against MRI-derived markers of the earliest preclinical atherosclerotic changes.

II. Methods

A. In vivo Data

MRI scans were performed on a 3T scanner (Achieva, Philips Healthcare; Best, The Netherlands). The protocol included 3D time-of-flight, 3D contrast-enhanced magnetic resonance angiography (CE-MRA), phase contrast MRI (PC-MRI), and black blood MRI (BB-MRI). A CE-MRA was acquired following intravenous injection of gadolinium as contrast agent. Retrospectively-gated, 2D cine PC-MRI images were acquired prior to contrast injection and placed transverse to the nominal long axis of the common carotid artery (CCA) and, in a separate acquisition, through the internal and external carotid arteries (ICA and ECA, respectively). Further details of the CE-MRA and PC-MRI protocols are provided elsewhere [2].

BB-MRI images were acquired both before and after the CE-MRA at the CCA and at the carotid bifurcation. To measure WT, the inner and outer wall boundaries were segmented from the pre- and post-contrast BB-MRI images at the CCA, and for the ICA at the first slice distal to the flow divider (FD), a standard location hereafter referred to as FD+1. The contours were used to compute WT at 12 equally-spaced sectors. Contrast enhancement (CE) was computed as the relative change in sector intensities from the pre to post-contrast BB-MRI images. CCA-WT and CCA-CE were defined as the respective maximum values from the 12 sectors. For ICA-WT and ICA-CE, we determined the maxima from the FD+1 slice data.

B. Computational Hemodynamics

In lumen segmentation from CE-MRA, all 42 cases included the proximal CCA to at least five diameters upstream of the bifurcation. Subject-specific flow rate waveforms were extracted from the cine PC-MRI series. Computational hemodynamics simulations were carried out [3]. We computed three established descriptors of low and oscillatory shear, i.e. the time-averaged wall shear stress magnitude (TAWSS), oscillatory shear index (OSI), and relative residence time (RRT). Data from all 42 simulated cases were pooled to identify the upper (lower) 20th percentile value of OSI, and RRT (TAWSS). For each CFD model, branches were split into CCA and ICA segments. For each segment, the surface area exposed to OSI, RRT above (or TAWSS below) its respective threshold value was calculated, and divided by the respective segment's surface area. These variables, reflecting the relative area exposed to disturbed flow associated with a particular hemodynamic descriptor, are denoted as LSA (low shear area), OSA (oscillatory shear area), RTA (residence time area).

Pearson linear regressions were used to identify relationships between each hemodynamic variable and either WT or CE. Multiple regressions were used to control for cardiovascular risk factors independently correlated with WT or CE. Regressions are reported as the individual standardized correlation coefficient (β) and *P*-value.

ISBN: 978-88-6296-000-7

III. Results

Age and hypertension were used to adjust CCA-WT in subsequent (multiple) linear regressions. HDL concentration was used to adjust ICA-WT. Neither ICA-CE nor CCA-CE was correlated with any cardiovascular risk factors.

The complete set of 42 reconstructed carotid bifurcation geometries, showing LSA, is presented in Figure 1. As summarized in Table I, a significant and segment-specific association between wall thickening and OSA at the CCA (β=0.311, *P*=0.031) and ICA (β=0.343, *P*=0.022), but no other hemodynamic variable, was observed. CE at the ICA, on the other hand, was strongly associated with LSA (β=0.533, *P*=0.0003) and RTA (β=0.489, *P*=0.001) at that segment. CCA-CE was not associated with any hemodynamic variable.

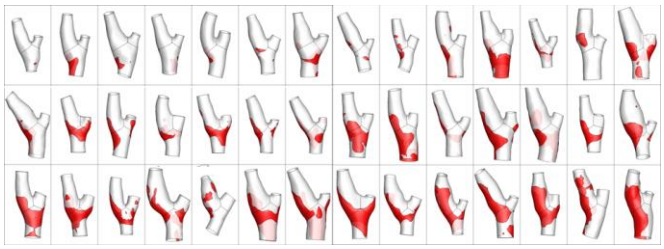

Figure 1. Maps of WSS for all 42 cases outlining LSA, ordered from lowest (top left) to highest (bottom right) LSA.

IV. Discussion

The presented results indicate that LSA is associated with increased contrast uptake at the carotid bulb, as measured by CE at the ICA, whereas high OSI (and not LSA) is associated with increased bulb WT. As no significant correlation was found between WT and CE, in the atherosclerosis initiation process they represent different aspects, which we demonstrate to be linked to distinct hemodynamic disturbances. Since the processes resulting in an increased gadolinium uptake precede wall thickening and frank atheroma formation [4], low WSS appears to be an earlier marker of atherosclerotic changes than high OSI, at least in the subclinical individuals studied here. This advocates against the common conflation of the terms "low" and "oscillatory" WSS in the context of early atherosclerosis studies at the carotid bifurcation. Notably, our data indicate that oscillatory WSS affects a later stage in atherosclerosis than low WSS, namely wall thickening.

The presented association between LSA and CE at the carotid bulb is consistent with the idea of CE being an early marker of EC dysfunction caused by flow stagnation, a flow condition characterized by low WSS. In fact, low WSS has been reported to increase EC permeability by inducing non-physiological EC turnover, and increasing the presence of leaky junctions [5]. Such WSS-mediated processes on ECs would naturally increase contrast agent uptake from the luminal side into the vessel wall. On the other hand, neovascularization from adventitial vasa vasorum may also be postulated as a reason for increased CE. In fact, ample evidence supports the occurrence of neovascularization as the initial stage of atherosclerotic disease, occurring before the development of atherosclerotic plaque [2]. The dominant stimulus is relative hypoxia and the associated local oxidative stress. It has been previously demonstrated that hypoxic conditions at the vessel wall occur in regions of the carotid bifurcation characterized by low WSS conditions [2].

TABLE I - **P*<0.05; ***P*<0.001.

Hemodynamic	*Wall Thickness*		*Contrast Enhancement*	
Variables	*CCA*	*ICA*	*CCA*	*ICA*
CCA - LSA	β = 0.116	β = 0.094	β = -0.066	β = 0.141
CCA - OSA	**β = 0.311***	β = 0.272	β = -0.101	β = 0.030
CCA - RTA	β = 0.241	β = 0.180	β = -0.109	β = 0.146
ICA - LSA	β = 0.208	β = 0.155	β = 0.028	**β = 0.533****
ICA - OSA	β = 0.177	**β = 0.343***	β = -0.106	β = 0.217
ICA - RTA	β = 0.272	β = 0.248	β = -0.001	**β = 0.489****

Standardized coefficients (β) from linear regressions of hemodynamic variables *vs*. wall thickness or contrast enhancement. Bold and superscripts highlight significant regressions.

Although it is not possible in our study to separate these sources of augmented CE uptake, the present relation ultimately suggests a connection between both mechanisms. In fact, LSA in the bifurcation implies a slowly recirculating flow, providing, concurrently: *i*) the cue for inflammatory changes underlying EC permeability increase; and *ii*) a fluid mechanical barrier to oxygen transport, exposing EC and in general the vessel wall to hypoxic conditions, which in turn stimulate adventitial vasa vasorum neovascularization.

V. Conclusion

Low WSS and oscillatory WSS appear to associated with different facets of early atherosclerosis at the carotid artery. From the present results, low WSS is associated with increased contrast uptake, while oscillatory WSS is associated with increased wall thickening. Since the processes resulting in an increased contrast uptake precede wall thickening, low WSS magnitude may be considered an earlier "local" risk marker for atherosclerotic changes than oscillatory (or indeed low and oscillatory) WSS.

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