Carotid plaque stenosis, metabolism and flow dynamics: Important determinants of atherosclerotic risk?

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To date, the treatment algorithm of a symptomatic carotid artery stenosis is still based on the anatomical degree of stenosis. With a number-needed-to-treat of six to prevent one stroke through the next 5-years in patients with a > 70% stenosis, five out of six of these patients are exposed to surgical risks without having the benefits.[1] Also, in patients receiving best medical treatment, related to their stenosis-degree, an ipsilateral stroke does occur within 5-years in 7.8%.[2] This clearly indicates that novel imaging modalities are needed to improve the decision-making process for patients with a carotid artery stenosis.

Takami et al. have performed a retrospective analysis of 20 patients that were treated for a symptomatic carotid artery stenosis.[3] They used Magnetic Resonance Angiography (MRA) as an input parameter for a computational fluid dynamics (CFD) analysis and subsequently the maximum Wall Shear Stress (WSSmax) was related to the degree of stenosis and to the measured metabolic activity of the plaque on ^{18}F-FDG PET/CT. Significant correlations were observed between the WSSmax and degree stenosis ($\rho = 0.81$, $P < 0.001$), WSSmax and the maximum target-to-blood pool ratio (TBRmax) ($\rho = 0.64$, $P < 0.001$), and also the TBRmax and degree of stenosis ($\rho = 0.50$, $P = 0.001$). These observations highlight that blood flow patterns correlate to biological processes in the vessel wall and to atherosclerotic disease development. Risks of a carotid artery stenosis on becoming symptomatic can therefore not be judged appropriately by the degree of stenosis only.

The authors have taken the WSSmax as the critical flow-related parameter in this study. The relation between flow and its related parameters is well known and extremely complex in itself as it depends on various parameters, including the vascular geometry and flow velocities and directions. Various flow-related parameters can be calculated of which the WSS is the most well-known. A low WSS promotes atherosclerosis by stimulating inflammatory processes, plaque initiation and growth. A low sustaining WSS has been related to destabilization of non-obstructive high-risk plaques while an obstructive high risk plaques destabilizes at the most stenotic site under high WSS conditions, or at the upstream shoulder and downstream parts by low WSS.[4] Large oscillations in the blood flow, that can be quantified as the Oscillatory Shear Index, are also associated with progression of atherosclerosis.[5] The most relevant parameter for the risk of stroke in patients with a carotid artery stenosis is yet to be defined.

The optimal method of flow visualization is also matter of debate. In the current study MRA-based computational fluid dynamics (CFD) was chosen. A major drawback of this choice is the fact that that CFD requires a multitude of assumptions inducing various

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uncertainties and a potential bias. The use of duplex velocities as boundary conditions might have provided a more realistic flow pattern. For future studies also the use of phase contrast MRI could also be of value, avoiding the use of theoretical input parameters. This technique, however, is rather time-consuming and costly limiting its clinical applicability. As an alternative, novel ultrafast ultrasound imaging techniques, with up to 10.000 images/sec, could be used to estimate blood flow velocity vectors within the carotid artery.[6,7] The feasibility of this method has previously been shown in the carotid artery bifurcation of both healthy subjects and patients, with a proven reproducibility for the estimated velocity fields.[8] The further development of this technique might facilitate the implementation of flow-based decision making in clinical practice.

In the current study it was demonstrated that the correlation coefficient of the relationship between WSSmax and TBRmax was higher than that between degree of carotid artery stenosis and the TBRmax.[3] In addition, the mean TBRmax was higher in symptomatic carotid artery stenoses as compared to asymptomatic stenoses, supporting the pivotal role of inflammation in the development of unstable carotid plaques, as confirmed in previous studies.[9,10] ^{18}F-FDG is a commonly used tracer that enters cells with high glycolytic metabolic requirements, including activated inflammatory cells, which express high levels of glucose transporters. Increased ^{18}F-FDG uptake in carotid plaque demonstrates a direct association with plaque macrophage infiltration leading to its use as a surrogate of vascular inflammation, but the signal is relative low and aspecific.[9] New PET radiopharmaceuticals against other important plaque biological targets with higher signal are needed and applicable now. For example ^{18}F-SodiumFluoride (^{18}F-NaF) for detection of micro-calcification in vulnerable atherosclerotic plaques,[11] or targeted against vulnerable unstable neo-angiogenesis, which promotes intraplaque hemorrhage.[12,13] Additionally the introduction of digital PET significantly improves the sensitivity and resolution of the camera system.[14] This is of particular interest in future studies to improve carotid plaque imaging, resulting in higher signal and better heterogeneity delineation.

The study of Takami et al. has provided us with further support to the hypothesis that flow-related forces could be of utmost importance in biological, inflammatory metabolic processes within a carotid plaque and that they could be decisive in the development of unstable plaques.[3] In order to develop a reliable and more personalized treatment algorithm for patients with a carotid artery stenosis further studies on this subject are clearly indicated and cut-off values of unstable plaques for the multimodality approach need to be identified. Both flow patterns and biological process should then be taken into account in relation to both each other and to plaque growth and destabilization. Eventually this should lead to a better risk assessment of patients with a carotid stenosis and consequently an improved decision-making algorithm for invasive treatment. This would prevent unnecessary interventions, reduce the stroke rate in this subset of patients, whilst reducing costs.

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