A Journey Into the Carotid Artery Microenvironment in High Resolution

Challenging the Stenosis–Symptoms Paradigm*

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Atherosclerosis is the most frequent cause of extracranial cerebrovascular disease, and represents an important cause of stroke and transient ischemic attack, being responsible for up to 15% to 20% of all ischemic strokes (1). Carotid artery stenosis has long been recognized as an important risk factor. In most studies of carotid artery stenosis intervention, clinically important stenosis, beyond which point the stroke risk is increased, are those greater than 50% to 60% diameter stenosis (2). Patients with asymptomatic carotid stenosis are at increased annual risk (2% to 5%) for ipsilateral carotid territory ischemic stroke (3,4).

However, although a clear correlation between the degree of stenosis and the risk of stroke in symptomatic patients was demonstrated in the NASCET trial (North American Symptomatic Carotid Endarterectomy Trial) (5), this association was less clear in asymptomatic patients (6–10). In fact, the pathophysiology of ipsilateral stroke in patients with carotid artery stenosis goes far beyond the degree of stenosis, with several other mechanisms involved: 1) artery-to-artery embolism of thrombus formed on the atherosclerotic plaque; 2) atheroembolism of cholesterol crystals or other atheromatous debris; 3) acute thrombotic occlusion of an extracranial artery resulting from plaque rupture; and 4) structural disintegration of the arterial wall resulting from dissection or subintimal hematoma. Furthermore, reduced cerebral perfusion resulting from critical stenosis or occlusion caused by progressive plaque growth needs the intracranial collateral circulation to be deficient for neurological symptoms to occur (1). This knowledge, along with data from several randomized trials showing low rates of neurological events in asymptomatic patients with moderate-to-severe carotid stenosis (8,9), point to the fact that the degree of carotid stenosis is probably not the most important measurement of interest, but rather the morphology and composition of the carotid plaques are.

Therefore, other aspects of carotid lesions have been explored as potential markers of plaque vulnerability and stroke risk. Several noninvasive and invasive imaging modalities have shown the ability in small studies (11–13) to characterize different plaque components and morphologies, such as positive remodeling, lipid content, ulceration, echolucency, and intraplaque hemorrhage. However, the prognostic value of such findings has yet to be determined in prospective and adequately sized studies. Limited axial resolution of these imaging methods also hampers the identification of some important aspects of plaque vulnerability (e.g., inflammation, fibrous cap thickness, plaque rupture, intraluminal thrombus) and contributes to the difficult task of identifying the so-called vulnerable carotid plaques that would benefit from invasive treatment, before neurological events happen. As a result, symptomatic status and severity of carotid stenosis still form the basis for current guideline recommendations for carotid revascularization (1).

In this issue of JACC: Cardiovascular Interventions, Jones et al. (14) investigated carotid plaque characteristics with intravascular optical coherence tomography (OCT) in 49 symptomatic (n = 27) and asymptomatic (n = 22) patients. In this pioneering work, the authors take advantage of the superior axial resolution of OCT (~10 μm) and expand our knowledge of the carotid artery microenvironment, providing important insights regarding carotid stenosis quantification and plaque characterization. They also provide reassuring information about the safety and feasibility of performing OCT studies in the carotid circulation, acquiring images of adequate quality for interpretation, with no need of balloon occlusion or cerebral protection devices.

The accuracy of OCT for lumen quantification has been extensively described. In in vitro studies using phantom models of known dimensions as references, OCT provided lumen area measurements closer to the actual phantom dimensions than did IVUS, and with less variability, positioning OCT as the most accurate modality for lumen dimension quantification in vivo.

In the coronary territory, quantitative angiography underestimated lumen areas by about 5%, whereas IVUS overestimated it by 9% when compared with OCT (15). This slight variability can explain some of the results presented by Jones et al. (14). Although a high correlation was seen between the diameter stenosis measurements derived by quantitative angiography and OCT (r = 0.93, p < 0.001), an unacceptably high variability (40%)
between the 2 methods was documented in cases where revascularization decisions had been taken by angiography or OCT. Based on the American Heart Association (AHA) criteria for revascularization of ≥60% stenosis for asymptomatic patients and ≥50% stenosis for symptomatic patients, 29% of the carotid lesions that would be revascularized on the basis of angiographic quantification of stenosis severity would have their treatment deferred on the basis of the OCT results; an additional 11% of the lesions that would not be revascularized by angiography would be treated on the basis of OCT quantification. These figures reinforce the limitations of angiography for stenosis severity quantification.

Furthermore, the authors confirmed the stenosis–symptom paradox, with asymptomatic individuals presenting greater median diameter stenosis than symptomatic patients by angiography (67% vs. 39%, p = 0.004), with a trend in the same direction by OCT (66% vs. 42%, p = 0.098). Importantly, no correlations were observed between carotid diameter stenosis and the presence of symptoms (p = 0.10), even after the exclusion of symptomatic patients with nonsignificant carotid narrowings (p = 0.33).

Beyond precise lumen quantification, the high resolution of OCT allows for accurate characterization of plaque components, and identification of features of plaque vulnerability such as lipid-rich plaques, fibrous cap thickness, thin-cap fibroatheromas (TCFA), vascular inflammation, plaque rupture, plaque erosion, and intravascular thrombus (16–20). Benefiting from the unprecedented resolution of OCT among all in vivo imaging modalities, Jones et al. (14) elegantly used OCT to reproduce, in vivo, the AHA classification scheme of atherosclerosis derived from histopathology, assessing carotid plaques for the presence of “complicated” features known to be associated with adverse clinical events: 1) ruptured TCFA; 2) intraluminal thrombus; and 3) ruptured calcified nodule. They found that symptomatic patients had a significantly higher frequency of complicated plaques than asymptomatic patients (74.1% vs. 36.4%, p = 0.02), with intraluminal thrombus (odds ratio: 3.49, 95% confidence interval: 1.04 to 11.3, p = 0.037) and ruptured TCFA (odds ratio: 4.35, 95% confidence interval: 1.03 to 18.3, p = 0.045) emerging as independent predictors of symptomatic status by logistic regression analysis. Interestingly, complicated plaque features were evenly distributed in stenoses smaller than or >50% by OCT. Another important contribution from the current work is the report that more than one-third of asymptomatic patients have high-risk carotid plaques, potentially being at increased risk of stroke, irrespective of stenosis severity. Once again, the stenosis–symptoms paradigm has been challenged.

It is also important to highlight that most of the plaque characteristics for classification assessed in the current work were assumed from histopathology validation of OCT in coronary arteries. One should keep in mind that atherosclerotic plaques in the carotid territory do not exhibit the same composition and morphology as seen in coronary arteries, likely as a consequence of different sizes, spatial orientation, and flow dynamics.

The main difference between carotid artery plaques and coronary plaques is the higher prevalence of intraplaque hemorrhage in the former: in symptomatic patients, 65% of the carotid plaques showed signs of intraplaque hemorrhage (21). The prevalence of calcifications is equivalent for carotid and coronary plaques, although more calcified nodules were present in the carotid territory. From a morphological perspective, carotid plaques often have smaller necrotic cores and thicker fibrous caps. Lumen cavities, rarely seen in coronary arteries, are often observed in carotid plaques, likely originating from a ruptured cap covering a small necrotic core (22). The good news is that OCT can be used to detect and quantify most of the compositional and morphological characteristics of atherosclerotic plaques in both the carotid and coronary circulation. As pointed out by the investigators (14), intraplaque hemorrhage, an important marker of plaque progression, may be difficult to recognize by OCT because of the light attenuation that makes differentiation from lipid pools challenging. By contrast, intimal microvessels, which have also been linked to coronary plaque progression and may be a source for blood extravasation and intraplaque hemorrhage, can be easily identified by OCT, and serve as a potential indirect marker of vulnerability.

As we reach the end of this journey into the carotid microenvironment, we leave it with 1 certainty. Neurological symptoms and risk of stroke are more to do with plaque composition and morphology, rather than with the degree of stenosis, which can serve, though, as an important marker of disease burden. Lastly, this journey raises several doubts that need to be further explored in future prospective studies: what is the prognostic impact of such “complicated” plaques detected by OCT? What is the fibrous cap thickness that best predicts carotid artery rupture? What is the best management strategy for these high-risk carotid plaques? What is the risk of intervening (percutaneously or surgically) on those lesions, and what plaques are going to benefit most from mechanical intervention?

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