Low-Density Carotid Plaques and the Risk of Stroke

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ABSTRACT

Ischemic stroke is the second cause of death worldwide, and at least a quarter of all ischemic strokes are associated with carotid atherosclerotic disease, the diagnosis of which relies primarily on imaging methods. Traditional risk assessment in carotid atherosclerotic disease has long been based on the measurement of stenosis severity, but there is strong evidence that only stenosis grading falls short in predicting near-future events. Moreover, numerous histopathologic studies gathered increasing evidence that plaque vulnerability depends on its composition and morphology; therefore, the new concept of "vulnerable plaque" analysis is necessary, independent of the carotid narrowing. Follow-up studies concluded that the presence of a large-lipid necrotic core and thin fibrous cap are significantly more likely to result in future ischemic events and thereby are hallmarks for unstable lesions. Under these conditions, magnetic resonance imaging (MRI) and multi-detector computed tomography (MDCT) characterization of specific plaque properties can provide additional information on ischemic stroke risk that are not provided by the simple measurement of luminal stenosis. Therefore, besides the stenosis degree, plaque morphology assessment using noninvasive methods could be useful to identify rupture-prone plaques and may be a suitable prognosis tool that will help improve risk stratification and the effectiveness of therapeutic strategies.

Keywords: carotid atherosclerotic disease, vulnerable plaque, thin fibrous cap, lipid-rich necrotic core, stenosis degree, magnetic resonance imaging

INTRODUCTION

Carotid atherosclerotic disease represents a major modern health problem; it is a well-known cause of ischemic stroke, causing about 10–20% of strokes or transient ischemic attacks (TIA).¹ According to the World Health Organization (WHO), stroke is one of the leading reasons of mortality in Western countries and the second most frequent cause of mortality in developed nations, accounting for about one for every 16 deaths in the United States. By 2020 it is estimated that almost 25 million people will die from cardiovascular disease.²

Besides the high risk of death, stroke represents the leading cause of long-term acquired disability in adults, even where advanced healthcare is available,
as 60% of those who suffer a stroke become dependent, 40% of victims require special care, and 9% require total care.\textsuperscript{3,4}

Moreover, the global burden of atherosclerosis will continue to rise in the future due to population aging and consequently its clinical and social implications.\textsuperscript{5} These dismal statistics and the high cost of treatment for stroke should direct attention towards focusing more on stroke prevention.\textsuperscript{6}

Carotid artery atherosclerosis is more frequent in men than in women, and its prevalence increases with age, but overall, women have more ischemic events due to stroke than men.\textsuperscript{5}

**ATHEROSCLEROTIC PLAQUE MORPHOLOGY AND THE CONCEPT OF VULNERABLE CAROTID ARTERY PLAQUE**

Atherosclerotic plaques located on carotid arteries are comparable to those encountered in various arterial locations.\textsuperscript{5} The major site of involvement in atherosclerotic disease is the carotid bulb, and carotid atherosclerosis in Caucasian subjects is most commonly located at the carotid artery bifurcation, typically involving the distal common carotid and the proximal internal carotid artery. At least fifteen percent of all strokes can be accredited to carotid bifurcation atherosclerotic plaques and, to a lesser extent, the proximal external carotid artery.\textsuperscript{1,7}

The percentage of carotid narrowing is the most used criteria for identifying high-risk stroke patients, but current research has concluded that traditional risk assessment based on stenosis grade alone is insufficient to predict near-future events in subjects with vulnerable carotid artery lesions, a series of studies estimating that approximately 50% of lesions are vulnerable. Therefore, stenosis grade alone ignores the influence of the type of plaque and thus may not accurately predict the risk for ischemic complications.\textsuperscript{3}

Besides the hemodynamic significance, carotid atherosclerotic plaques have embolicigenic properties, with an important role in the pathogenesis of ischemic stroke.\textsuperscript{8} From a pathogenic point of view, the arterio-arterial embolism mechanism defines ischemic stroke as a complication of vulnerable plaques. The formation and detachment of embolic particles from an atherosclerotic plaque and their subsequent transportation to the intracranial circulation causes vascular occlusion and occurrence of neurological symptoms.

Carotid plaque characteristics other than the degree of stenosis represent important factors of vulnerability that are involved in the occurrence of neurological symptoms. Features such as plaque composition are responsible for almost half of the stroke cases, thus justifying the introduction of the “vulnerable plaque” concept.\textsuperscript{9} An increased lipid-rich necrotic core and a thin fibrous cap (TFC) are the most common features found in vulnerable plaques associated with high risk of thromboembolic ischemic events. Numerous studies have shown the association between the presence of TFC and plaque rupture, therefore the presence of TFC is considered an independent risk factor for ischemic events. Mughal M \textit{et al.} found that fibrous cap thinning was present in 95% of symptomatic plaques and 48% of asymptomatic plaques.\textsuperscript{5}

A large lipid necrotic core (LRNC) is the second important symbol of plaque vulnerability. As the LRNC is the main part of the plaque, a larger LRNC has been linked with ruptured TFC in both symptomatic and asymptomatic carotid atherosclerosis, and pathological studies concluded that a larger lipid volume destabilizes carotid atherosclerotic plaques, making them more prone to embolization.\textsuperscript{10} In fact, a larger volume of LRNC is associated with plaque rupture, while a decreased volume is more expected to undergo erosion. A recent study, which followed plaque characteristics and the risk of stroke, concluded that plaques with a lipid necrotic core as a dominant component had a sevenfold increased risk of stroke in acute coronary syndrome patients.\textsuperscript{11}

Plaque instability is also influenced by gender differences, men presenting both a thinner fibrous cap and a larger LRNC when compared to women.\textsuperscript{7}

Therefore, there is accumulating evidence from follow-up studies demonstrating that carotid atherosclerotic plaque composition determines its future vulnerability and thereby the risk of cerebrovascular ischemic events.

**HIGH RISK PROFILE BEYOND LUMINAL STENOSIS GRADING**

It is a well-known fact that, in clinical practice, asymptomatic revascularizations far outnumber symptomatic revascularizations, thus showing a considerable overtreatment. On the other hand, even with the current standard tools of risk stratification, the annual risk of ischemic events in selected patients with high-risk features only reaches 10%.\textsuperscript{8}

Clinically, at this moment the quantification of luminal stenosis with the use of angiographic techniques is considered the most effective strategy for the evaluation of atherosclerotic disease severity. The results of numerous recent studies have shown that vulnerable plaques may occur even in low-grade stenotic lesions.\textsuperscript{12,13} Furthermore,
two large trials (the Asymptomatic Carotid Atherosclerosis Study — ACAS and the Asymptomatic Carotid Surgery Trial — ACST) have failed to find any strong evidence regarding stenosis severity being a predictor for increased risk of stroke. Based on these facts, it is clear that an assessment based only on stenosis severity criteria it is not a sensitive or specific marker for the risk of stroke, and underestimates the burden of the lesions, as well as their severity, including those cases in which the lesions appear harmless.

Moreover, currently there is no agreement on managing subjects with a moderate carotid stenosis and recent onset of neurological symptoms. Several clinical studies have concluded that half of individuals with new ischemic events have a mild-to-moderate carotid narrowing. Furthermore, most of the echocardiographic follow-up studies have demonstrated that most cardiovascular and cerebrovascular events are encountered in patients with stenotic lesions that reduce the lumen diameter to less than 70%; therefore, this group of individuals is alleged to have incipient carotid atherosclerosis and no indication of surgical or interventional treatment, despite having a high-risk profile for subsequent ischemic events. Consequently, identifying high-risk features of ischemic events in such patients is more complicated than originally thought.

A more rational approach based on a better risk-profiling is necessary, in order to warrant new imaging tools for identifying features beyond luminal stenosis that are important predictors of future ischemic events. This task is considered both crucial and challenging, as it will reduce unnecessary interventions in those patients who actually need it, while also lowering the thromboembolic risk.

**Duplex Ultrasound**

Duplex ultrasound is the most important noninvasive imaging tool that allows an accurate measurement of significant carotid stenosis. Compared with arteriography, Duplex ultrasound also generates a high-resolution B-mode ultrasound image, which allows visualization of the vessel lumen, as well as the size and composition of the atherosclerotic lesions, for a better assessment of morphologic characteristics besides the degree of stenosis. Therefore, the ultrasound evaluation of carotid plaques includes two different characteristics, size and echogenicity, and both have been proved as strong predictors of cardiovascular events. Based on this, a study conducted by Polak J et al. revealed an increased incidence of ischemic events in patients with echolucent plaques. Moreover, asymptomatic echolucent lesions are correlated with an increased number of asymptomatic embolic events in the cerebral territory supplied by the middle cerebral artery.

Several studies have shown that vulnerable carotid lesions with ipsilateral neurological symptoms share common echocardiographic features, being more echolucent and heterogeneous, in contrast with stable plaques, which are often asymptomatic and uniformly hypoechoic/hyperechoic.

A large-scale clinical study conducted by Reiter et al. demonstrated that an increased echolucency in the carotid lesions during a short-term interval is an important predictor of mid-term major adverse cardiovascular events (MACE) in high-risk individuals, independent of traditional risk factors or the degree of artery stenosis. Those results suggest that repeated ultrasonographic measurements of carotid plaques in 6 to 9 months, could identify patients at an increased risk for near-future events.

The ultrasonic internal structure of a carotid plaque is a factor that contributes in a major way to the development of cerebrovascular outcomes. Therefore, ultrasonic characterization of carotid plaques may have the ability to expand the risk assessment of such patients.

**Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) is a relatively new investigation tool that allows not only quantification of plaque burden on the carotid arteries, but it also characterizes the compositional features of carotid atherosclerotic plaques. Several prospective studies using this imaging tool have revealed significant differences in the composition and morphology of symptomatic and asymptomatic plaques, features beyond luminal stenosis, including the presence of calcification, a large necrotic plaque core, or a thin fibrous cap. Plaques with such features are more likely to cause symptoms and seem to be predictive for future thromboembolic ischemic events. Numerous prospective MRI studies based on serial examinations in individuals with moderate carotid stenosis (50–70%) have shown a strong correlation between these vulnerable plaque features and the development of subsequent ischemic neurological events. These results have been validated by histological studies, which have proved that plaque characteristics obtained by MRI imaging correlate well with the histopathological aspect, according to the American Heart Association (AHA) classification.
over, these features were found on a greater scale among men compared with women.30

MRI studies have also concluded that high-risk plaque characteristics are prevalent even in carotid branches that have minimal narrowing. Sam et al. found that 1/3 of asymptomatic patients with 50–79% stenosis and 10% of patients with 16–49% stenosis present cap rupture.31 In a recent study, Dong et al. found a surprisingly high prevalence of complex atherosclerotic plaques in carotid arteries with no stenosis.32 Therefore, in vivo MRI is able to discriminate between the specific histological subtype of carotid plaque as proposed by the AHA, thus being able to stratify intermediate to advanced carotid atherosclerotic lesions and distinguish between vulnerable and stable plaques.8,33

The main advantages of this imaging tool include, beyond extensive histological validation for carotid atherosclerotic plaque characterization, its superior specificity for tissue composition assessment and the lack of ionizing radiation exposure during the procedure.

Overall, carotid MRI determination of plaque composition deserves further attention and could represent a useful tool in risk stratification of stroke in asymptomatic or recently symptomatic patients with moderate stenosis, based on its potential prognostic value for subsequent ischemic events.

**MULTI-DETECTOR COMPUTED TOMOGRAPHY ANGIOGRAPHY**

Multi-detector computed tomography angiography (MDCTA) is a widely available imaging-based tool that allows a reliable evaluation of carotid steno-occlusive disease.34 This technique can also quantify distinct lesion components and plaque volume.18,35 Previous studies based on this technique have demonstrated a strong relationship between plaque composition and further ischemic events in symptomatic carotid stenosis (>50%) and low degree lesions (0% to 49%). In all these studies, the large lipid necrotic core and thin fibrous tissue assessed by MDCTA were identified as the strongest determinants for plaque ulceration. Interestingly, a major proportion of vulnerable plaques were located in symptomatic low-degree stenoses.26,28 Hence, a better assessment is necessary in these patients, in order to detect rupture-prone plaques and potentially improve risk stratification.

Overall, these findings demonstrate that the assessment of carotid plaque composition that predispose to ischemic events via MDCTA, apart from the degree of stenosis, could have a key role in risk stratification for lesion instability and stroke events.

**CONCLUSIONS**

Atherosclerotic lesions in the carotid arteries are commonly encountered in medical practice. Duplex ultrasound usually guides the therapeutic decision-making process between pharmacological, interventional, or surgical treatment and plays a critical role in existing treatment guidelines. Recent studies concluded that carotid atherosclerosis is, beyond the degree of stenosis, a more complex problem, and carotid lesion characteristics, such as the presence of a lipid-rich necrotic core and a thin fibrous cap, describe the so-called “vulnerable plaques”, which tend to rupture, presenting a high risk of subsequent thromboembolic ischemic events.

Performing a risk stratification based only on the measurement of carotid stenosis via sonographic investigation is insufficient, as it ignores the influence of plaque type. Therefore, the development of better risk-profile assessment methods is needed. Noninvasive imaging investigations via MRI or MDCTA, validated by numerous studies, can identify plaque components with a high risk of ischemic events, thus reducing unnecessary healthcare costs in patients with stable plaques, leading to an appropriate referral of patients with high-risk lesions to surgery or stenting procedures.

A better understanding of the characteristics of vulnerable plaques and a closer investigation of plaque components and morphology will provide a foundation for further research on the pathogenesis of high-risk lesions.

**CONFLICT OF INTEREST**

Nothing to declare.

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