Pericarotid Fat as a Marker of Cerebrovascular Risk

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ABSTRACT

SUMMARY: Vascular inflammation is widely recognized as an important factor in the atherosclerotic process, particularly in terms of plaque development and progression. Conventional tests, such as measuring circulating inflammatory biomarkers, lack the precision to identify specific areas of vascular inflammation. In this context, noninvasive imaging modalities can detect perivascular fat changes, serving as a marker of vascular inflammation. This review aims to provide a comprehensive overview of the key concepts related to perivascular carotid fat and its pathophysiology. Additionally, we examine the existing literature on the association of pericarotid fat with features of plaque vulnerability and cerebrovascular events. Finally, we scrutinize the advantages and limitations of the noninvasive assessment of pericarotid fat.

ABBREVIATIONS: AI = artificial intelligence; AUC = area under the curve; HU = Hounsfield unit; PCF = pericarotid fat; PVAT = perivascular adipose tissue; US = ultrasound; USPIO = ultra-small superparamagnetic iron oxide particles

Carotid artery atherosclerosis, a complex and multifactorial systemic condition, is highly prevalent in the general population and is a well-established risk factor for adverse cardiovascular events worldwide.[1] Growing evidence suggests that vulnerable carotid plaques are associated with a higher risk of cerebrovascular events beyond the mere degree of carotid artery stenosis.[2] With regard to features of plaque vulnerability, inflammation is an integral element of the pathophysiologic processes that form the basis of atherosclerosis.[3-5] Inflammatory mediators are contained in the perivascular adipose tissue (PVAT), that is anatomically close to the vascular wall.[6] During atherosclerosis, local PVAT, adjacent to the carotid arteries, namely pericarotid fat (PCF), changes its composition and biology due to inflammatory processes with a "cross-talk" between PVAT and blood vessels.[7]

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The levels of systemic inflammatory serum markers can assist in identifying and detecting inflammatory responses,[8,9] but cannot discriminate specific areas of vascular inflammation.

Noninvasive imaging modalities have shown the feasibility of measuring PVAT and its alterations during atherosclerosis.[10-14] Among them, CT has been demonstrated to be capable to detect the inflammation-induced changes in perivascular carotid fat tissue due to an increase in Hounsfield units (HUs).[14] Several clinical studies have demonstrated the association of PCF and cerebrovascular events.[15-18] Fig 1 provides a graphic overview of the potential association of dysfunctional PCF.

This review aims to summarize the key concepts related to PCF and its pathophysiology, examining the existing literature on its applicability as a marker of plaque vulnerability and cerebrovascular events. Finally, we examine the advantages and limitations of the noninvasive assessment of PCF.

PATHOPHYSIOLOGY OF PERIVASCULAR CAROTID FAT

PCF represents the PVAT located adjacent to the carotid arteries.[19] PVAT consists of different cell types, mainly perivascular adipocytes, endothelial cells, and smooth muscle cells and is a metabolically active tissue surrounding most vascular beds, with some differences in large and small vessels. Indeed, in large vessels, PVAT is continuous with adventitial layers, while in small vessels it is an integral component of the vascular wall itself.[20] The lack of an anatomic barrier implies that mediators released by perivascular adipocytes can easily penetrate the blood vessel wall.[6,21]

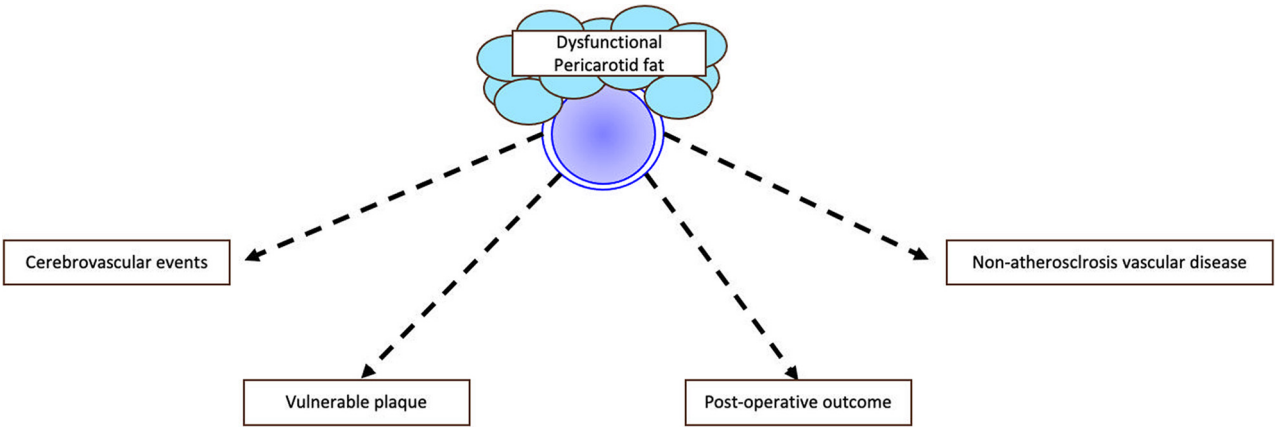

FIG 1. Graphic overview of potential association of dysfunctional PCF.

Growing evidence emphasizes the association between vascular inflammation and carotid atherosclerosis, from early atherogenesis to the progression of atherosclerotic lesions. The pathogenesis of atherosclerosis involves multiple steps that appear to be initiated by the deposition of low-density lipoproteins in the arterial intima, accompanied by local oxidative stress and immune and inflammatory activation.[22] Endothelial and smooth muscle cells respond to such conditions by expressing chemical mediators and recruiting macrophages which, in turn, accumulate intracellular lipids forming pathologic intimal thickening with lipid pools, namely fatty streaks, the first macroscopic sign of atherosclerosis.[22] Lesion progression occurs with accumulation of inflammatory leukocytes consisting primarily of macrophages and lymphocytes. Adhesion of monocytes involves the expression of selectins, which facilitate the rolling of white cells, followed by firm attachment to endothelial integrins mediated by immunoglobulin G superfamily members such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, and transmigration by way of the endothelial junctional proteins. During atherosclerosis, local PVAT undergoes alterations in its composition and biology, resulting in a shift in the secretome of PVAT.[6,23,24] Dysfunctional PVAT secretes a range of bioactive molecules, including adipokines and cytokines, which promote the activation of inflammatory pathways through paracrine and vasocrine effects. This, in turn, leads to endothelial dysfunction and further promotes inflammation.[18,23,25-27] Histologic studies have confirmed a marked increase in inflammatory cells in PVAT surrounding atherosclerotic vessels.[24,28-30] Furthermore, dysfunctional PVAT may be potentially linked to nonatherosclerosis vessel diseases through vascular wall inflammation, oxidative stress, vascular smooth muscle cell proliferation, and endothelial dysfunction.[31,32]

Quantifying the presence and extent of perivascular inflammation is emerging as a promising approach to predict cerebrovascular events and could lead to the development of personalized medicine with new therapeutic targets. The significance of vascular inflammation was underscored in the newly proposed Plaque-RADS score, which recommends reporting vascular inflammation as an ancillary feature.[4]

NONINVASIVE EVALUATION OF PCF

CT is a highly noninvasive sensitive technique for the comprehensive assessment of PCF, because of its availability and spatial resolution. It allows differentiation of tissue components based on different attenuation via HUs. It is well-established that CT attenuation for adipose tissue ranges from −190 to −30 HU. Inflammatory changes in the fat tissue may lead to impaired lipid development, resulting in less negative HU values.[33] Adipose tissue attenuation can be manually measured in CT angiography by defining a circular/elliptical region of interest close to the point of maximum stenosis while avoiding neighboring tissues such as muscle and venous vessels,[34] or semiautomatically through dedicated postprocessing software (Fig 2).[15]

CT enables the assessment of carotid anatomy and the identification of carotid plaques simultaneously,[34] and the quantification of PCF attenuation does not require extra protocol within routine carotid CT.

In addition to CT assessment of PCF, alternative modalities have been suggested. Skilton et al[35] developed a noninvasive ultrasound (US) parameter, called carotid extra-media thickness, defined as "the distance between the carotid media-adventitia interface and the jugular lumen." Despite this, PCF represents a considerable percentage of extra-media thickness measurement, as demonstrated in histologic specimens.[18] This proposed US parameter is not a direct measurement of PCF, because it also includes interstitial tissue, carotid artery adventitia, and the venous wall.[35] These novel proposed US parameters demonstrated notable association with vascular changes associated with cardiovascular risk factors.[35] Another US vascular index, namely periarterial adipose tissue intima media adventitia, has been introduced that incorporates carotid indexes (eg, intima-media thickness and extra-media thickness) and echocardiography parameters (eg, epicardial fat thickness).[36] This new US parameter has been demonstrated to be associated with the presence and severity of cardiovascular events.[36]

Other noninvasive imaging modalities have been proposed to directly evaluate the inflammatory state in carotid plaques rather than the PCF, serving as an indirect marker of plaque inflammation. In particular, promising results in the assessment of plaque inflammation are obtained by using MR imaging with ultra-small

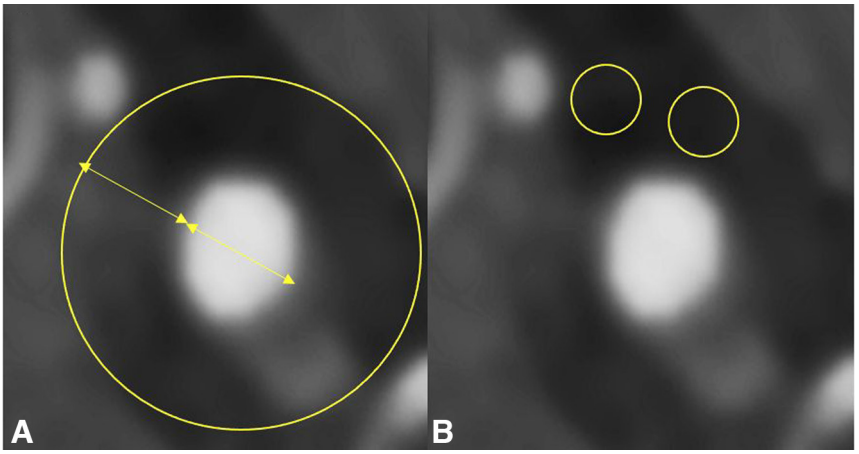

FIG 2. Examples of various methods described in the literature to define PCF. *A*, PCF is defined as the adipose tissue within a radial distance from the outer vessel wall equal to the diameter of the carotid vessel. *B*, PCF was obtained by tracking 2 separate regions of interest (each with an area of 2.5 mm^2) located at least 1 mm from the outer margin of the carotid artery wall.

superparamagnetic iron oxide particles (USPIO).[10-12] USPIO uptake measured by MR imaging has been demonstrated to correlate with the number of macrophages, as in vivo imaging biomarkers for plaque inflammation and vascularity in histologic studies.[12,37]

Similarly, [^{18}FDG]-PET holds promise to identify areas of inflammation.[13] Johnsrud et al[38] demonstrated that ^{18}FDG uptake reflects the inflammatory status as assessed on histology. Indeed, activated macrophages during an inflammatory state have high glucose metabolism and radioactive ^{18}FDG is absorbed by macrophages in excised human plaque.[39] Encouraging findings are arising from the application of ^{18}F-sodium fluoride PET in identifying active formation of calcification linked to plaque vulnerability.[40-44]

Current Limitations of Noninvasive Imaging Modalities

The assessment of PCF as an indirect marker of vascular inflammation presents intrinsic limitations associated with each noninvasive imaging technique. For instance, PCF measurement by using CT has several limitations related to CT parameters including reconstruction algorithm, CT model, and tube voltage.[45,46] As reported by Ma et al,[47] PVAT demonstrated a positive linear association with tube voltage, suggesting that differences in tube voltage can lead to significant changes in HU values. Because carotid CT scans are acquired at various tube voltages depending on patient characteristics and the CT reconstruction system (which allows for the reduction of radiation and contrast medium volume), adjustments to threshold values for PVAT may be necessary. In addition, measurement approaches for PCF exhibit significant heterogeneity, and a standardized method for measuring and quantifying PCF has not yet been developed. Additionally, CT disadvantages include exposure to ionizing radiation and potential adverse reactions to iodinated contrast media.[48]

Conversely, US assessment, aside from its inability to exclusively target the PCF component, is subject to intrinsic limitations. These include interobserver variability, challenges related to plaque composition (such as calcifications), anatomic considerations, and constraints imposed by a limited anatomic window.[2,48,49]

Despite promising results in directly evaluating the vascular inflammatory status, the applicability of MR imaging with USPIO and [^{18}F]FDG-PET is limited in clinical practice due to long acquisition times, the need for specialized hardware for high-resolution images, the complexity of interpretation, as well as their expense and limited accessibility.[50]

ASSOCIATION WITH FEATURES OF PLAQUE VULNERABILITY

Inflammation is recognized as a crucial contributor to atherosclerotic plaque formation and destabilization and PCF contributes in promoting atherosclerosis by secreting proatherogenic mediators.[51,52] In the retrospective study of Yu et al,[16] 71 patients with carotid atherosclerosis were evaluated by using CT to analyze the relationship between PCF and various risk characteristics of carotid plaque, including American Heart Association type VI, intraplaque hemorrhage, thinning and/or rupture of the fibrous cap, lipid-rich necrotic core, and calcification. The PCF attenuation ipsilateral to vulnerable plaque showed increased values in comparison with the contralateral carotid. PCF attenuation was an independent predictor for intraplaque hemorrhage (β = 0.529, $P < .001$) in multiple regression analysis. The researchers proposed that para-endocrine pathways secrete inflammatory cytokines, leading to increased vascular oxidation and inflammation, which in turn enhances microvascular permeability. This process may contribute to subsequent intraplaque neovessel rupture.[16] The association between PCF and intraplaque hemorrhage was also reported by Zhang et al.[19] The authors evaluated inflammatory changes in PCF by using CT in 72 patients with carotid atherosclerosis.[19] PCF surrounding plaques with intraplaque hemorrhage demonstrated higher HU values than those without (-41.4 ± 3.9 versus -55.8 ± 6.5 HU; $P < .001$). This observation was independent of age, calcification, degree of stenosis, maximum plaque thickness, and ulceration (OR, 1.96; 95% CI, 1.41–2.73; $P < .001$).[19] Similar results were described by Liu et al[53] who demonstrated that PCF is an independent risk factor for plaque vulnerability (OR, 1.212; 95% CI, 1.074–1.367; $P = .002$). Additionally, PCF attenuation was significantly associated with the degree of hypertension, a well-known risk factor for atherosclerosis and cardiovascular and cerebrovascular events.[53]

ASSOCIATION WITH CEREBROVASCULAR ISCHEMIC EVENTS

Several studies have demonstrated the association of cerebrovascular events and perivascular carotid fat (Online Supplemental Data).[15,17,53-57] Baradaran et al[17] reported a higher PCF attenuation

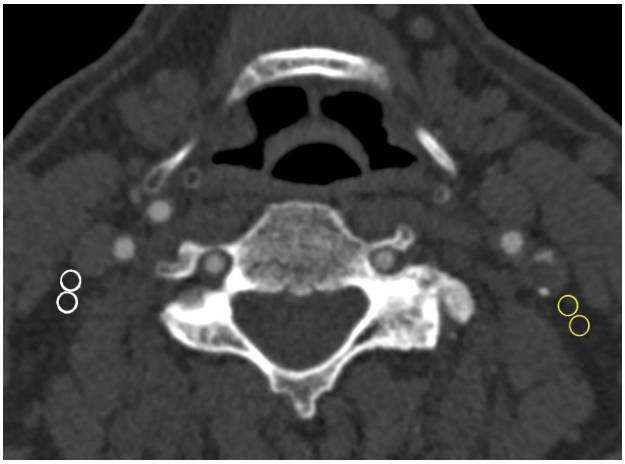

FIG 3. Axial CT image of a 71-year-old-man with left ischemic stroke. Two ROIs were positioned in the PCF surrounding a stenotic left internal carotid artery with a vulnerable plaque (*yellow circles*), and 2 ROIs were placed in the contralateral carotid artery in the same section (*white circles*) to measure perivascular fat attenuation. The PCF demonstrates an HU value of 58.3 and 61 in the left carotid artery and 75.2 and 78.5 in the right carotid artery, respectively.

in carotid arteries ipsilateral to a stroke or transient ischemic attack in comparison with asymptomatic carotid arteries.

Similar results were also reported by Liu et al[53] in their retrospective study of 80 patients with carotid atherosclerosis with moderate-to-severe stenosis. Patients with altered PCF demonstrated larger infarct core volume, faster infarct core growth rate, and worse outcome.[53] The link between cerebrovascular events and PCF was also explored in the study by Zhang et al.[15] Symptomatic carotid plaques demonstrated higher PCF HU values than those without symptoms (−55.0 ± 10.0 versus −68.0 ± 10.3 HU, $P < .001$).[15] In multivariate logistic regression after adjusting for confounding factors (eg, hyperlipidemia, statin use, antiplatelet use, calcification, degree of luminal stenosis, maximum plaque thickness, and ulceration), PCF attenuation remained significantly associated with cerebrovascular symptoms (OR, 1.13; 95% CI, 1.07–1.19; $P < .001$).[15] In addition, PCF attenuation showed excellent diagnostic performance in discriminating between symptomatic and asymptomatic plaques with an area under the curve (AUC), sensitivity and specificity of 0.81, 87.3%, and 60.6%, respectively.[15]

Saba et al[14] investigated the inflammatory changes in the fat tissue surrounding the carotid artery in 100 patients with carotid artery stenosis by using CT, demonstrating a statistically significant positive correlation between perivascular fat attenuation and contrast plaque enhancement on CT ($\rho = 0.6582$, $P = .001$). In addition, symptomatic patients showed a stronger correlation compared with asymptomatic patients ($\rho = 0.7052$, $P = .001$ versus $\rho = 0.4092$, $P = .001$), suggesting that perivascular fat attenuation may be an additional indirect marker of plaque instability in the carotid arteries.[14]

Increased attenuation in the fat surrounding the carotid artery was also reported in patients with embolic stroke of undetermined source. Hu et al[58] evaluated 126 patients with embolic stroke of undetermined source and 118 patients with ischemic stroke from large artery atherosclerosis by using brain MR imaging and CT, reporting that the perivascular carotid fat attenuation around the carotid artery ipsilateral to ischemic stroke significantly increased in comparison with contralateral carotid in both patients with embolic stroke of undetermined source (−56.31 ± 18.70 versus −67.31 ± 20.01, $P = .000$) and in patients with large artery atherosclerosis ischemic stroke (−51.62 ± 19.95 versus −64.58 ± 22.68, $P = .000$).[58] Additionally, the authors reported no significant difference between ipsilateral and contralateral PCF attenuation to infarct in both patients with embolic stroke of undetermined source and in patients with large artery atherosclerosis ischemic stroke. These findings indicate the presence of an inflammation extending beyond the vessel lumen in patients with embolic stroke of undetermined source who share similar risk factor profiles with those experiencing large artery atherosclerosis strokes.[58]

PCF may potentially demonstrate influences on the response to intravenous fibrinolysis, as highlighted in a recent study by Gencer et al.[59] The authors explored the association of PCF and intravenous tissue plasminogen activator through logistic regression models in 174 patients with acute ischemic stroke treated with intravenous tissue plasminogen activator. The study reported that PCF attenuation was an independent predictor for both modified Rankin score 0–2 and mRS 0–1 outcome.[59]

In addition, PCF attenuation measured by CT has been shown to improve risk stratification for obstructive coronary artery stenosis beyond the Framingham risk score and the degree of carotid artery stenosis in patients who have experienced acute ischemic stroke or transient ischemic attack (Fig 3).[60]

ASSOCIATION WITH POSTOPERATIVE INTERVENTIONAL COMPLICATION/OUTCOME

PCF may potentially demonstrate effect on postoperative complication of interventional carotid treatment. Hu et al[61] evaluated 181 patients with carotid atherosclerosis who underwent carotid artery stent placement and followed them for 2 years in the postoperative period. Patients with early in-stent restenosis (defined as ≥50% of the luminal stenosis occurring at the entire length of the stent or within 3 mm of the stent edge) showed higher mean HU of PCF attenuation in comparison with patients who did not experience in-stent restenosis (−42.26 ± 6.81 versus −59.66 ± 10.75; $P < .001$). This observation was independent of age, sex, traditional risk factors, predilation and postdilation (OR, 1.353; 95% CI, 1.215–1.506; $P < .001$).[61] In addition, the authors identified the best cutoff value for predicting the occurrence of early in-stent restenosis with an AUC of 0.912, a sensitivity of 97.67%, and specificity of 69.57%.[61] Similarly, Jin et al[62] evaluated the changes in PCF by using CT in 183 patients treated with mechanical thrombectomy due to anterior circulation large vessel occlusion. The authors reported that higher perivascular carotid fat was associated with unsuccessful recanalization (adjusted OR, 2.968; 95% CI, 1.292–6.819; $P = .010$), poor outcome (adjusted OR, 2.704; 95% CI, 1.610–4.541; $P < .001$), and mortality (adjusted OR, 1.894; 95% CI, 1.040–3.449; $P = .037$) after adjustment in multivariate analysis.[63] Overall, these findings suggest that PCF may serve as an additional marker in treatment and prevention strategies for carotid atherosclerosis diseases. This relationship may be linked to local oxidative stress promoted by PCF

after invasive carotid treatment, leading to the secretion of proinflammatory factors, vascular smooth muscle cell dysfunction, and accelerated neointimal hyperplasia.[61]

ASSOCIATION WITH NONATHEROSCLEROTIC CAROTID VASCULAR DISEASE

Growing evidence suggests that PVAT plays a key role also in nonatherosclerotic vascular disease. PVAT reacts to mechanical injuries within the arterial endothelium and regulates the subsequent development of neointima by influencing factors that promote the growth of smooth muscle, adventitial inflammation, and neovascularization.[63] Experimental in vivo approaches using adipose tissue transplantation have demonstrated that PVAT accelerated neointimal hyperplasia, adventitial macrophage infiltration, and adventitial angiogenesis in carotid arteries.[64] Based on histopathologic studies, inflammatory mediators in PVAT may also play a role in the pathogenesis of artery dissection.[65-67] In a study by Cheng et al,[68] the attenuation of PCF was significantly higher in patients with carotid artery dissection compared with those without (-58.7 ± 10.2 versus -69.3 ± 9.3 HU, $P < .0001$). In addition, patients with carotid dissection demonstrated a significant reduction in the attenuation of PCF compared with the baseline scan during a median follow-up of 108 days (-57.5 ± 13.4 to -74.3 ± 10.5 HU, $P < .05$). The researchers proposed that the increased inflammation surrounding carotid arteries could contribute to the mechanical stress on arteries, leading to the development of carotid artery dissection.[68] It has been recognized that PVAT participates in vasculitis pathogenesis. Recently, a prospective cohort study was performed to evaluate the characteristics and significance of PVAT in Takayasu arteritis. The authors found that PVAT had 100% sensitivity and 95% specificity for differentiating active Takayasu arteritis from controls with an AUC of 0.99.[69]

FUTURE DIRECTION: ARTIFICIAL INTELLIGENCE AND RADIOMICS

The application of artificial intelligence (AI) in carotid artery imaging can help in detecting vulnerable plaque features, enhancing decision-making regarding invasive procedures and treatments in cardiovascular care. Several AI models have been proposed to automatically segment carotid arteries, facilitating the assessment of plaque burden and PCF.[70-72] AI models have the potential to address several existing limitations in the noninvasive assessment of PCF. Notably, they can mitigate the lengthy analysis time typically associated with manual evaluation and reduce interobserver variability, thereby enhancing the efficiency and reliability of PCF assessment. In addition, AI models can integrate imaging data, incorporating PCF along with demographics and clinical parameters, opening a new frontier in cardiovascular risk stratification, as demonstrated in coronary arteries.[73] AI-based approaches could streamline the noninvasive assessment of PCF and its application in clinical practice, reducing diagnostic time and enabling automatic classification of patients at risk. In recent years, radiomics features have been suggested as an additional tool to characterize features of plaque vulnerability, extracting voxel-based information from images, capturing the inherent complexity and heterogeneity of pixels in relation to their spatial "neighbors."[74] Radiomics extracts extensive quantitative information from conventional imaging data, identifying patterns that may not be discernible to a human reader. Therefore, radiomic analysis of PCF may offer more comprehensive insights into the biologic variations of PCF during carotid atherosclerosis.

CONCLUSIONS

The noninvasive assessment of PCF holds promise as an imaging marker, offering insights into carotid atherosclerosis and enhancing risk stratification. The role of PCF in carotid inflammation and plaque progression is crucial due to its bidirectional connection with carotid arteries. CT attenuation-based assessment of PCF shows promise in predicting high-risk plaques, cerebrovascular events, and postprocedural outcomes. Additionally, PCF may contribute to spontaneous carotid dissection and vasculitis. Despite its potential, challenges exist in standardizing PCF measurement across different CT systems. Standardization efforts are needed to integrate PCF assessment into clinical practice effectively. Future trials should focus on standardizing CT parameters to confirm the potential of PCF for risk assessment and guiding preventive measures.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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