Perivascular Fat Density and Contrast Plaque Enhancement: Does a Correlation Exist?


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ABSTRACT

BACKGROUND AND PURPOSE: Inflammatory changes in the fat tissue surrounding the coronary arteries have been associated with coronary artery disease and high-risk vulnerable plaques. Our aim was to investigate possible correlations between the presence and degree of perivascular fat density and a marker of vulnerable carotid plaque, namely contrast plaque enhancement on CTA.

MATERIALS AND METHODS: One-hundred patients (76 men, 24 women; mean age, 69 years) who underwent CT angiography for investigation of carotid artery stenosis were retrospectively analyzed. Contrast plaque enhancement and perivascular fat density were measured in 100 carotid arteries, and values were stratified according to symptomatic (ipsilateral-to-cerebrovascular symptoms)/asymptomatic status (carotid artery with the most severe degree of stenosis). Correlation coefficients (Pearson ρ product moment) were calculated between the contrast plaque enhancement and perivascular fat density. The differences among the correlation ρ values were calculated using the Fisher r-to-z transformation. Mann-Whitney analysis was also calculated to test differences between the groups.

RESULTS: There was a statistically significant positive correlation between contrast plaque enhancement and perivascular fat density (ρ value = 0.6582, P value = .001). The correlation was stronger for symptomatic rather than asymptomatic patients (ρ value = 0.7052, P value = .001 versus ρ value = 0.4092, P value = .001).

CONCLUSIONS: There was a positive association between perivascular fat density and contrast plaque enhancement on CTA. This correlation was stronger for symptomatic rather than asymptomatic patients. Our results suggest that perivascular fat density could be used as an indirect marker of plaque instability.

ABBREVIATIONS: CPE = contrast plaque enhancement; PFD = perivascular fat density

About one third proportion of ischemic strokes are caused by emboli from large-artery atherosclerosis usually involving the carotid artery.1-3 Traditionally, the degree of carotid stenosis is the main factor affecting therapeutic decisions. However, in recent years, similar to work in the coronary field, it has become clear that plaque composition plays a very important role in the occurrence of cerebrovascular events.3-6 The different parameters associated with increased vulnerability include a lipid-rich necrotic core,7 intraplaque hemorrhage,8,9 and contrast plaque enhancement (CPE).10 In particular, CPE is a surrogate marker of microvessel density within the carotid plaque, and it is associated with plaque inflammation.11,12 Inflammatory changes in the fat tissue surrounding the coronary arteries have been associated with coronary artery disease and high-risk,13 vulnerable plaques, and in the past few years, some studies have investigated the perivascular fat density (PFD), measured as the density of pericoronary adipose tissue, as a parameter for coronary plaque evaluation.14,15 These articles showed that PFD was increased around culprit lesions compared with nonculprit lesions of patients with acute coronary syndrome. An increased PFD was recently described also in high-risk vulnerable carotid atherosclerotic plaque.16 In this study, we investigated the hypothesis that there is a correlation between the presence and degree of PFD and CPE.
MATERIALS AND METHODS

Study Design and Patient Population

Institutional review board (University of Cagliari) approval was obtained, and informed consent was waived because of the retrospective nature of the study. To identify the minimum cohort size as having statistically significant data, we performed a power calculation (type I error, \( \alpha = .10 \); type II error, \( \beta = 0.15 \); difference between correlation values = 0.2) in which we estimated that a sample size of at least 93 carotid arteries would be sufficient to investigate the potential correlation between CPE and PFD. We further increased the number of carotid arteries, and we studied a total number of 100 arteries from 100 patients (76 men, 24 women; mean age, 70 years; age range, 46–87 years).

Included were consecutive adult subjects who underwent CTA for suspected atherosclerotic disease of the carotid arteries from March 2016 to June 2017. Exclusion criteria included subjects younger than 18 years of age; CTAs performed for reasons other than suspected atherosclerotic disease (ie, dissection); and other etiologies for ischemic stroke such as evidence of a cardiac embolic source, evidence of an embolism from the thoracic aorta, and evidence of vertebrobasilar artery disease.

According to a standardized protocol, CTA of the carotid artery was performed for the following reasons: 1) Carotid sonography showed a significant stenosis (>50% measured according to NASCET criteria) or features of plaque vulnerability (ulcerations, irregular surface), and 2) carotid sonography could not adequately assess the degree of stenosis and plaque characteristics because of anatomic conditions. Moreover, all subjects presenting with acute cerebrovascular events underwent CTA of the carotid arteries at the time of their acute CT of the head.

Part of the population (n = 56) of this study was included in previously published study on carotid plaque composition.

Classification of Cerebrovascular Symptoms

In this study, both symptomatic and asymptomatic patients were considered, and only 1 carotid artery for each patient was included in the analysis. For asymptomatic patients, the carotid artery with the most severe degree of stenosis was included, whereas in symptomatic subjects, the carotid artery ipsilateral to the neurologic symptoms (eg, left hemispheric stroke, left carotid artery) was considered.

Patients were classified into symptomatic or asymptomatic patients as documented by the treating neurologist using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. We considered the plaque to be calcified, and this category of plaque was considered in the case of dense calcifications. First, the contrast material datasets were assessed in a circular or elliptic ROI (≥1 mm²; Fig 1) in the predominant area of the plaque to measure the Hounsfield unit values according to the method described by Saba et al. Areas showing contamination by contrast material or calcifications and regions of beam-hardening were excluded. In cases in which 50% of the plaque contained calcium components, we considered the plaque to be calcified, and this category of plaque was excluded.

To obtain a correct registration between basal and postcontrast phases, radiologists visually assessed the corresponding slices when it was necessary to select another section along the z-axis, the so-called matching process.

The section used was recorded to calculate the difference between the basal and contrast phase along the z-axis. Following this matching phase, an ROI of the same area as that used in the contrast phase was put in the same position on the plaque to measure the basal Hounsfield unit value. The CPE is the difference in Hounsfield unit values obtained between the postcontrast and basal ROIs.

Perivascular Fat Density Analysis

The assessment of the PFD was performed by 2 radiologists in consensus 1 month later than the CPE quantification according to the approach described by Baradaran et al. The pixels
corresponding to adipose tissue were identified, and 2 ROIs (each 2.5 mm²) were placed in the perivascular fat present on the same axial section showing the maximal NASCET-defined ICA stenosis, and the averaged values were considered. The site of ROI placement was not exactly the same for each subject and was determined at the maximum stenosis site, location of the carotid plaque, and location of the perivascular fat pads. ROIs were drawn carefully to include only detectable fat density (visually dark and confirmed by negative Hounsfield units). Care was taken to exclude the carotid artery wall or surrounding soft-tissue structures, with ROIs placed at least 1 mm from the outer margin of the carotid artery wall. The process was re-checked before final acceptance.

Statistical Analysis
The normality of each continuous variable group was tested using the Kolmogorov-Smirnov Z-test. Continuous data were described as mean ± SD, and binary variables were summarized as count (percentage). Correlation coefficients (Pearson r product moment) were calculated between the CPE and PFD. The differences among the correlation r values were calculated using the Fisher r-to-z transformation. Mann-Whitney analysis was also calculated to test the differences between the groups. A P value < .05 indicated statistical significance, and all correlation values were calculated using a 2-tailed significance level. R statistical and computing software (www.r-project.org) was used for statistical analyses.

RESULTS
Baseline Characteristics
Sixty-three patients had bilateral plaques, and 27 had unilateral plaques. Thirty-one patients were symptomatic for cerebrovascular symptoms, and 69, asymptomatic. Clinical and demographic characteristics are summarized in Table 1. The average length of the plaque was 22 ± 12 mm, and the average maximum wall thickness was 5.1 ± 1.8 mm. The average degree of stenosis was 61% (minimum, 3%; maximum, 94%). Thirty-nine carotid arteries had a NASCET stenosis of >50% (mean degree of stenosis, 64%; minimum, 50%; maximum, 94%). The summary values of the CPE and PFD are in the On-line Table.

Carotid Plaque Enhancement and Perivascular Fat Density Correlation Analysis
We found a positive correlation between CPE and PFD (Fig 2) (r value = 0.6582, P value = .001). In the separate analysis of symptomatic and asymptomatic patients, symptomatic patients showed a stronger correlation compared with asymptomatic patients (r value = 0.7052, P value = .001 versus r value = 0.4092, P value = .001).

In a second model of analysis, carotid plaques without CPE were excluded (n = 34), and a significant positive correlation between CPE and PFD was observed (r value = 0.7043, P value = .001) (Fig 2). Similar to the first analysis, there was a stronger correlation in symptomatic than in asymptomatic patients (r value = 0.7052, P value = .001 versus r value = 0.4092, P value = .001).

There was a significant difference in the r values (CPE and PFD) between symptomatic and asymptomatic patients by considering the entire cohort of 100 patients (zeta statistic = -1.9904; P value = .0465). However, after excluding the 34 cases in which CPE was not detected, there was no significance in the r values (zeta statistic = -0.4312; P value = .664).

Table 1: Demographics (n = 100 patients)

<table>
<thead>
<tr>
<th></th>
<th>Complete Cohort (n = 100)</th>
<th>Symptomatic (n = 31)</th>
<th>Asymptomatic (n = 69)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>69 y (46–87)</td>
<td>69.2</td>
<td>64.2</td>
<td>.037</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>76 (76%)</td>
<td>42 (75%)</td>
<td>34 (77.2%)</td>
<td>.792</td>
</tr>
<tr>
<td>Degree of stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>45%</td>
<td>26 (46%)</td>
<td>19 (44%)</td>
<td>.746</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>49%</td>
<td>30 (53.6%)</td>
<td>19 (43.4%)</td>
<td>.302</td>
</tr>
<tr>
<td>Smoking status</td>
<td>35%</td>
<td>23 (41.1%)</td>
<td>12 (27%)</td>
<td>.151</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23%</td>
<td>15 (26.8%)</td>
<td>8 (18.2%)</td>
<td>.312</td>
</tr>
<tr>
<td>Lipids</td>
<td>59%</td>
<td>35 (62.5%)</td>
<td>24 (54.6%)</td>
<td>.422</td>
</tr>
</tbody>
</table>

FIG 1. A 75-year-old man with right TIA. The basal scan (A) shows plaque (white arrow) of 32.93 HU, whereas the postcontrast scan (B) shows a plaque density (white arrow) value of 43.76 HU with a CPE of 10.83 HU. The PFD (white open arrow, C) was −77.545 HU.
Table 2 confirms a statistically significant difference in CPE and PFD according to the symptomatic or asymptomatic status of the patient.

**DISCUSSION**

In a cohort of 100 patients who underwent CTA for investigation of atherosclerotic carotid disease, we found a positive association between PFD and CPE on CTA. The correlation was stronger for symptomatic rather than asymptomatic patients.

In recent years, there has been growing interest in identifying features related to carotid plaque “instability,” and several markers have been identified. Histopathologic studies have demonstrated that a common feature in vulnerable plaques is increased neovascularity and concomitant presence of inflammatory cells. These observations strongly suggest that one of the main pathways linked to plaque rupture is inflammation. Disruption of the plaque because of inflammatory and hemodynamic factors leads to ulceration and fissuring, which, in turn, result in loss of normal endothelium and luminal exposure of the necrotic lipid core. There is limited work on identification of objective markers of inflammation and instability in the carotid artery. Henrichot et al., in 2005, in a histopathologic study, showed that inflammatory changes in the fat tissue surrounding coronary arteries are associated with coronary artery disease and high-risk plaques. Recently, such changes have been shown to be detectable on CT imaging in coronary and carotid arteries.

Inflammation and plaque neovascularization are 2 closely interrelated phenomena. CT is reliable in the detection and grading of intraplaque neovascularization through CPE analysis. In our study, we investigated a correlation between the presence and degree of PFD and CPE. Indeed, we found a positive correlation between CPE and PFD, which, though present in both symptomatic and asymptomatic patients, was much stronger in symptomatic plaques (p value = 0.7052, P value = .001).

This finding confirms that pericarotid adipose tissue, which encases the carotid arteries without an intervening fascial barrier, is a metabolically and immunologically active fat deposit implicated in atherogenesis. The impact of the CT density was studied, in particular, for the association of cardiovascular events, and while a lower CT density of visceral and subcutaneous abdominal...
fat has been linked to a greater extent of cardiovascular events,^{30,31} in the Framingham Heart Study,^{31} the relationship between epicardial and paracardial fat density and high-risk plaque features is not well-understood.

Not all the carotid artery plaques show CPE, because intraplaque neovascularization can be absent depending on plaque type and characteristics. When we considered only carotid arteries showing CPE (n = 66), a statistically significant positive correlation between the CPE and PFD was maintained (Fig 2). After excluding plaques without CPE, an even stronger correlation between CPE and PFD was found in symptomatic than in asymptomatic patients. (\( \rho \) value = 0.6381, \( P \) value = .001 versus \( \rho \) value = 0.5663, \( P \) value = .001).

The differences among the correlation \( \rho \) values showed that the correlation between the CPE and PFD is not statistically stronger in symptomatic-versus-asymptomatic patients. This could be explained by the following: 1) The low number (38 versus 28 patients) does not allow reaching the statistically significant threshold, or 2) those plaques without CPE represent a confounding factor because of the 34 plaques that did not show CPE, only 3 cases were symptomatic.

We also found a statistically significant difference in CPE and PFD according to the symptomatic or asymptomatic status of the patient. These data are concordant with previous observations by Baradaran et al.,^{16} who found that symptomatic patients had a higher mean PFD compared with asymptomatic patients (−66.2 ± 19.2 versus −77.1 ± 20.4 HU, \( P \) value = .009), and by Saba et al.,^{17} who found a statistically significant difference between symptomatic and asymptomatic patients for the presence of CPE (\( P \) value = .001; OR = 7.5).

Our results are significant because they provide early validation of the use of PFD and/or CPE as noninvasive tools to assess inflammatory activity in carotid atherosclerotic disease. Further work is needed to understand the value of these biomarkers in predicting future cerebrovascular events or in identifying culprit plaques in patients with embolic strokes of undetermined sources. Furthermore, because PFD can be obtained on all CTA examinations while CPE requires both pre- and postcontrast imaging, future studies should aim to understand the incremental value of CPE above PFD alone, because in many centers, CTA is performed with a postcontrast acquisition alone. With further validation, these markers may be useful inclusion criteria for randomized trials incorporating anti-inflammatory stroke-prevention therapies in patients with carotid disease.

Our findings are concordant with ongoing research in the field of molecular imaging for the assessment of inflammation in atherosclerotic plaques, mainly performed with PET/CT,^{32,33} because of the potential to detect inflammation in plaques due to a high concentration of macrophages in such structures.^{34} Recent studies have shown that PET with [18F] NaF appears may be superior to [18F] FDG in detecting the types of microcalcification that are markers of inflammation and high-risk plaques.^{35} Thus, PET techniques may serve as a valuable complement to more routinely and easily acquired CT to help clinicians detect vulnerable carotid plaques or so-called culprit plaques that have already given rise to an embolic event. Recent advances in translational research using PET/CT have also enabled the visualization of perivascular inflammation in vulnerable atherosclerotic plaques.^{36,37}

Our study has limitations. It is a retrospective study, and our data need confirmation in a larger cohort and should be considered as preliminary results. Although suggesting that PFD could be a surrogate of plaque instability, we cannot distinguish whether there is a causative relationship between the 2 or whether PFD is a mere epiphenomenon of the adjacent atherosclerotic process. Nevertheless, our data indicate, for the first time in the carotid artery, that an objective measure such as PFD can be of value as an indirect marker of plaque instability.

**CONCLUSIONS**

In patients with carotid artery stenosis investigated by CTA, there is a correlation between perivascular fat density and contrast plaque enhancement. This correlation is stronger for symptomatic rather than asymptomatic patients. Our results indicate that PFD could be used as an objective indirect marker of plaque instability in the carotid arteries.

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