The Correlation between Calcium Volume and Carotid Artery Stenosis in Patients with Neurologic Symptoms

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ABSTRACT

Based on the strong correlation between calcium volume and carotid artery stenosis, some studies suggest using carotid calcium volume to diagnose carotid artery stenosis. However, a negligible correlation between calcium volume and carotid artery stenosis was found in symptomatic patients suspected of having carotid stenosis. The aim of this study was to further assess the reliability of using carotid calcium volume in the diagnosis of carotid artery stenosis in symptomatic patients.

We retrospectively examined the carotid CT angiography of 65 patients suspected of having carotid artery stenosis. The Pearson correlation coefficient (r) was used to evaluate the correlation between calcium volume and degree of carotid stenosis. Using calcium volume thresholds of 0.03 and 0.06 mL, the diagnostic performance of the calcium volume for determining a stenosis degree of ≥ 40% and ≥ 50% was investigated.

The calcium volume-based evaluation showed a weak correlation with the degree of stenosis on the symptomatic side (r=0.13, P=0.14) and a moderate correlation with the degree stenosis on the asymptomatic side (r=0.39, P<0.01). For both sides, there was a weak correlation (r=0.29, P<0.01) between calcium volume and degree of stenosis. To detect a stenosis of ≥ 40%, the sensitivity and specificity were 85% and 37%, respectively, for the volume threshold of 0.03 mL and 63% and 57%, respectively, for the volume threshold of 0.06 mL.

Similar to a previous study, we found a weak correlation between calcium volume and carotid artery stenosis in patients with neurologic symptoms. The results suggest that in this selected patient population, the evaluation of carotid artery stenosis may not be replaced by the calcium volume.

Carotid artery stenosis is one of the well-established risk factors for ischemic stroke. Previous studies showed that carotid endarterectomy has significant benefits for symptomatic patients with moderate to severe stenosis [1-4]. It is therefore important to have a diagnostic tool for precise assessment of the degree of stenosis. With the rapid scan time and non-invasive nature of computed tomography (CT), multislice helical CT angiography (CTA) has been increasingly used in the assessment of the degree of coronary and carotid artery stenosis [5-9].

Based on a strong correlation of calcium volume with degree of coronary artery stenosis, some studies have shown that a CT-based measurement of calcium volume may be used as a screening test for carotid atherosclerotic diseases [10, 11]. However, in a patient population with neurologic symptoms[12], the correlation of calcium volume with degree of stenosis was negligible and weak for the symptomatic and asymptomatic sides, respectively. These results differed in a study[10] of patients with suspected head and neck cancer and in a study[11] of trauma patients.
One possible explanation for the discrepant results was the patient selection [13].

The primary aim of this study was to verify whether the calcium volume can represent the degree of carotid stenosis in evaluating symptomatic patients with carotid atherosclerotic diseases. To precisely assess the degree of carotid artery stenosis and the volume of calcium, we conducted dual-energy carotid CTA studies of 65 patients with neurologic symptoms. Dual-energy CTA allows a differentiation of iodine-filled vessels from calcified plaques, making a more accurate measurement of calcified carotid plaque possible. Therefore, there was no need for an unenhanced CT scan in addition to the enhanced CT scan.

MATERIALS AND METHODS

Patient selection and CT imaging protocol

Sixty-five patients who had neurogenic symptoms (in all including: right-side weakness, left-side weakness, bilateral limb weakness, right hand tremor, left hand numbness, right visual loss, dizziness, headache, vertigo, syncope, dysphagia, slurred speech, and consciousness change.) were included in this study, and all of whom underwent duplex sonography. For patients with suspected carotid stenosis evaluated by duplex sonography, subsequent CTA examinations were performed using a second-generation dual source CT scanner (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany). For the injection of contrast medium, an 18-gauge intravenous catheter was placed in the antecubital vein. After an initial injection delay estimated by the bolus-tracking technique (threshold of 100 Hounsfield units), 100 mL of contrast (Iodixanol, Visipaque 320, GE Healthcare Ireland, Carrigtown, Ireland, or Iohexol, Omnipaque 350, GE Healthcare Ireland, Carrigtown, Ireland) was infused at a rate of 5 mL/s. Scanning was performed using a dual-energy mode with 2×32×0.6 collimation, a pitch of 0.9, rotation time of 0.28 second, and at 100 kV/150 ref mAs (Tube A) and Sn140 kV/178 ref mAs (Tube B). The scan ranged from the aortic arch up to the scalp. The CT images were reconstructed using the following parameters: a 0.6-mm slice thickness, a 0.3-mm increment and a medium smooth kernel (D26).

Measurements of stenosis and calcium volume

Stenosis measurements were performed by a radiologist on a dedicated workstation (Syngo MMWP VE 40, Siemens Medical Solutions). The image plane that was perpendicular to the axis of the vessel was used to determine luminal diameter. A radiologist measured the cross-sectional luminal diameter at the narrowest location and the normal internal carotid artery diameter at least 2 cm above the site of narrowing or plaque. Then, using North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria, the degree of carotid artery stenosis was quantified as minimal stenosis (0%-29%), mild stenosis (30%-49%), moderate stenosis (50%-69%), severe stenosis (70-99%) and occlusion (100%) [1].

As described previously [10], axial tomographic images within 2 cm below and above the carotid bifurcation were selected for measuring the volume of the carotid bifurcation calcium. Before the evaluation of calcification, automatic contrast medium removal was performed on the dual-energy images. On each axial image, a region of interest (ROI) intended for inclusion was manually drawn by a radiologist. Then, we used these ROIs to define a combined volume of interest (VOI). After defining the VOI, a volume evaluation function available on the workstation was used to automatically measure the calcium volume within the pre-defined VOI.

Statistical analysis

The correlation between the carotid calcium volume and the degree of carotid artery stenosis was determined by calculating the Pearson product-moment correlation coefficient (r), and a paired t-test was used to test the statistical significance of r. Similar to previous studies [10, 11], a 40% or greater luminal stenosis was considered to be significant. To obtain the best combination of sensitivity and specificity, we selected calcium volumes of 0.03 and 0.06 mL as thresholds for detecting a significant stenosis [10, 11]. Using calcium volume thresholds of 0.03 and 0.06 mL, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and receiver operating characteristic (ROC) curve of stenosis ≥ 40% were calculated. Since the benefit of carotid endarterectomy in patients with carotid stenosis greater than 50% is of benefit [4], we also calculated the sensitivity, specificity, PPV, NPV and ROC curve for stenosis ≥ 50%.

RESULTS

We calculated the mean value of calcium volume and its standard deviation (SD) for symptomatic, asymptomatic and all arteries and for the stenosis categories (Table 1). Of the 130 carotid arteries, 43 arteries were labeled as symptomatic and 87 as asymptomatic. Also, for 57 carotid arteries categorized as minimal stenosis, 20 arteries have a zero stenosis according to the NASCET criteria. We found a significant increase in calcium volume between minimal and mild stenosis and between minimal and severe stenosis only. In addition, the measured calcium volume was not found to be associated with carotid artery stenosis ≥ 30%. We did not observe a significant difference in measured calcium volume between the symptomatic and asymptomatic sides.

The Pearson correlation coefficient for all arteries was 0.29 (P < 0.01); the symptomatic side was 0.13 (P=0.14), and the asymptomatic side was 0.39 (P < 0.01). There was...
Carotid artery stenosis and calcium volume

Table 1. Group size (Symptomatic)

<table>
<thead>
<tr>
<th>Group size (Symptomatic)</th>
<th>Average Calcium Volume (mL)</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal (0-29%)</td>
<td>0.11 ± 0.18</td>
<td>0.08 ± 0.12</td>
<td>0.09 ± 0.14</td>
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</tr>
<tr>
<td>Mild (30-49%)</td>
<td>0.27 ± 0.27</td>
<td>0.23 ± 0.23</td>
<td>0.25 ± 0.24</td>
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</tr>
<tr>
<td>Moderate (50-69%)</td>
<td>0.13 ± 0.24</td>
<td>0.18 ± 0.17</td>
<td>0.16 ± 0.20</td>
<td></td>
</tr>
<tr>
<td>Severe (70-99%)</td>
<td>0.17 ± 0.24</td>
<td>0.31 ± 0.24</td>
<td>0.26 ± 0.24</td>
<td></td>
</tr>
<tr>
<td>Occlusion</td>
<td>1 (0)</td>
<td>0.04</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>130 (43)</td>
<td>0.16 ± 0.23</td>
<td>0.16 ± 0.19</td>
<td>0.16 ± 0.20</td>
</tr>
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</table>

Table 2. Pearson Coefficient

<table>
<thead>
<tr>
<th></th>
<th>Average calcium volume (mL)</th>
<th>Average stenosis degree (%)</th>
<th>Group size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>0.13</td>
<td>0.16 ± 0.23</td>
<td>43</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.39</td>
<td>0.16 ± 0.19</td>
<td>87</td>
</tr>
<tr>
<td>All</td>
<td>0.29</td>
<td>0.16 ± 0.20</td>
<td>130</td>
</tr>
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</table>

Table 3. Performance of the calcium volume test determining a stenosis degree of ≥ 40%

<table>
<thead>
<tr>
<th></th>
<th>Calcium volume threshold = 0.03 mL</th>
<th>Calcium volume threshold = 0.06 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptomatic</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>75%</td>
<td>92%</td>
</tr>
<tr>
<td>Specificity</td>
<td>26%</td>
<td>41%</td>
</tr>
<tr>
<td>PPV</td>
<td>56%</td>
<td>52%</td>
</tr>
<tr>
<td>NPV</td>
<td>45%</td>
<td>88%</td>
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</table>

no statistically significant difference in measured stenosis degree between the symptomatic and asymptomatic sides (Table 2).

Calcium volume tests were used to determine stenosis degrees of ≥ 40% and 50% (Tables 3 and 4). In general, the sensitivity was high when using a minimum threshold of 0.03 mL, but the specificity was low. We observed that both sensitivity and NPV decreased with increasing calcium volume thresholds, but both specificity and PPV increased with increasing calcium volume thresholds. Increasing the degree of stenosis resulted in a decrease in PPV and an increase in NPV. We also found that the sensitivity and specificity of the two tests (i.e. stenosis degrees of ≥ 40% and 50%) were similar. The ROC curves of various degrees of stenosis (i.e. ≥ 40% and 50%) showed similar findings (Fig. 1).
The coronary calcium volume score was first reported to be a reliable indicator of coronary artery stenosis [14-17], and was then applied to other arteries such as the carotid artery [10-12, 18]. However, using the volume of carotid bifurcation calcium as a screening tool for detecting carotid stenosis is controversial. A strong correlation between calcium volume and the degree of carotid stenosis was found in patients with either suspected head and neck cancer [10] or trauma [11], but a weak correlation was observed in symptomatic patients suspected of having carotid artery stenosis [12]. As pointed out in another study [13], the reason for this discrepant result may be patient populations. Since the study cited above [12] did not observe a strong correlation between the calcium volume and the degree of carotid stenosis, we wanted to confirm the findings by reproducing the same methods in a selected population.

Similar to the previous study [12], our study was conducted in a population of patients with neurologic symptoms. Our results showed a weak correlation between calcium volume and the degree of carotid stenosis (r=0.29). However, as in the previous study [12], we observed that two patients with a stenosis degree of approximately 50% had a large difference in calcium burden (Figs. 2,3). In addition, our study found lower sensitivity (63%), specificity (57%), PPV (56%) and NPV (65%) at the calcium threshold of 0.06 mL compared with previously reported sensitivity (87.5%), specificity (86.7%), PPV (70.0%) and NPV (95.1%) at the same calcium threshold [10]. Our findings were consistent with previous data [12] that suggested that the calcium volume-based evaluation may not be a reliable screening tool for estimating the degree of carotid stenosis in patients with neurologic symptoms.

We noted a number of differences between the symptomatic and asymptomatic sides. The use of the calcium volume as an indicator to assess luminal stenosis appeared to be more sensitive and specific in detecting stenosis of the carotid arteries on the asymptomatic side. The PPV of the symptomatic and asymptomatic sides ranged from 43% to 57%, implying that a large calcium burden on both sides is not associated with significant carotid artery stenosis (Tables 3 and 4). Besides, the NPV of the symptomatic side was lower than that of the asymptomatic side. Hence, for the asymptomatic side, the calcium volume would not be large in the absence of significant carotid stenosis. We also observed that there was no difference in the performance of the calcium volume test between significant stenosis of ≥ 40% and that of ≥ 50%.

Instead of single-energy CTA [10-12], dual-energy CTA was used to evaluate carotid stenosis and calcium volume. This is because dual-energy CTA provides several advantages over conventional single-energy CTA. First, dual-energy CTA makes automatic head bone and hard plaque removal possible and thereby improves lumen visualization as well as stenosis measurement [19-21]. Second, dual-energy CTA can be used to differentiate calcified plaques from iodine-filled lumen, providing a convenient and reliable way to measure calcium volume [22, 23]. As a result, manual adjustment of window/level settings can be avoided. Third, due to the elimination of the unenhanced CT scan, dual-energy CTA leads to a significant reduction in patient dose compared with conventional digital subtraction CTA [24].

For a patient population with suspected carotid artery stenosis, a weak correlation between calcified volumes and stenosis degree may be due to soft plaque and expansive artery remodeling [12]. A calcium volume score of 0.01 mL was found in a patient with severe stenosis (75%), which was caused by a buildup of soft plaque [12]. On the other hand, a calcium volume score of 0.55 mL was found in a patient with minimal stenosis (29%) which may be related to expansive artery remodeling [25, 26]. Hence, these two limiting factors should not be ignored when we perform the screening test (i.e. calcium volume measurement) in the general population.

**DISCUSSION**

The coronary calcium volume score was first reported to be a reliable indicator of coronary artery stenosis [14-17], and was then applied to other arteries such as the carotid artery [10-12, 18]. However, using the volume of carotid bifurcation calcium as a screening tool for detecting carotid stenosis is controversial. A strong correlation between calcium volume and the degree of carotid stenosis was found in patients with either suspected head and neck cancer [10] or trauma [11], but a weak correlation was observed in symptomatic patients suspected of having carotid artery stenosis [12]. As pointed out in another study [13], the reason for this discrepant result may be patient populations. Since the study cited above [12] did not observe a strong correlation between the calcium volume and the degree of carotid stenosis, we wanted to confirm the findings by reproducing the same methods in a selected population.

Similar to the previous study [12], our study was conducted in a population of patients with neurologic symptoms. Our results showed a weak correlation between calcium volume and the degree of carotid stenosis (r=0.29). However, as in the previous study [12], we observed that two patients with a stenosis degree of approximately 50% had a large difference in calcium burden (Figs. 2,3). In addition, our study found lower sensitivity (63%), specificity (57%), PPV (56%) and NPV (65%) at the calcium threshold of 0.06 mL compared with previously reported sensitivity (87.5%), specificity (86.7%), PPV (70.0%) and NPV (95.1%) at the same calcium threshold [10]. Our findings were consistent with previous data [12] that suggested that the calcium volume-based evaluation may not be a reliable screening tool for estimating the degree of carotid stenosis in patients with neurologic symptoms.

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**CONCLUSION**

Similar to the previously cited study [12], we found a weak correlation between the degree of carotid artery stenosis and calcium volume in a population of patients suspected of having carotid artery stenosis. The results

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**Table 4. Performance of the calcium volume test determining a stenosis degree of ≥ 50%**

<table>
<thead>
<tr>
<th>Calcium volume threshold = 0.03 mL</th>
<th>Calcium volume threshold = 0.06 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>75%</td>
</tr>
<tr>
<td>Specificity</td>
<td>26%</td>
</tr>
<tr>
<td>PPV</td>
<td>47%</td>
</tr>
<tr>
<td>NPV</td>
<td>55%</td>
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</table>
Figure 2. Illustration of the calcium volume measurement. First, the carotid bifurcation is sculpted. Then we subtract
the contrast medium. With the volume tool, the calcium volume is displayed. Then we use NASCET(diameter) and area to
measure its stenosis ratio. Case 1, NASCET: 54.1%, Calcium: 0.12 cm³.
Figure 3. Another illustration of calcium volume and stenosis. Case 2, NASCET: 50%, Calcium: 0.91cm³.
indicate that calcium volume cannot replace carotid stenosis degree in evaluating symptomatic patients with carotid atherosclerotic diseases.

We would like to especially thank Mr. Hsuan-Ming Huang, from Siemens company, for his participation and attribution in this paper.

REFERENCES