Calcified Carotid Plaques Show Double Symptomatic Peaks According to Agatston Calcium Score

Hiroyuki Katano, MD, PhD,*† Mitsuhito Mase, MD, PhD,* Yusuke Nishikawa, MD, PhD,* and Kazuo Yamada, MD, PhD*

Background: The precise mechanism of carotid calcification formation and its clinical significance including the difference in outcomes compared with coronary artery have not been clearly elucidated yet. We applied the calcium score for analyzing carotid plaque calcification in focus on its relationship with symptoms and discuss the difference in transitional patterns and the clinical outcome in comparison with calcified coronary plaques. *Methods:* Multidetector row computed tomography angiography was performed preoperatively to determine the Agatston calcium score, volume score, and Hounsfield values for a total of 330 carotid arteries from 194 patients. Analysis focused on the relation of "the symptomatic rate" to calcium score, volume score, and Hounsfield value as well as the characteristics of calcified plaques and coexisting diseases. The symptomatic rate of carotid artery plaques in each range of the index was calculated as the percentage of the number of carotid arteries with plaques, which elicited symptoms of the contralateral limbs or the ipsilateral retina to the whole number of carotid arteries with plaques within the range. *Results:* Calcified carotids with low symptomatic rate (<40%) tended to have calcification with significantly high calcium scores, high volume scores and mean/maximum Hounsfield values, high circularities, outer positions, positive remodeling, and carotid bulb/common carotid locations by univariate analysis, whereas high maximum Hounsfield value, high circularity, and outer position of calcification were significant independent predictors of low-symptomatic calcified carotid plaques by multivariate logistic regression analysis. When analyzed by calcium score, the rates for symptomatic carotids showed double peaks at calcium scores around 200-400 and 600-800 with a dip at 400-600. Significant independent predictors of low symptomatic carotid artery were high maximum Hounsfield value (odds ratio [OR], 5.70; $P = .005$), calcification encircling the carotid perimeter (OR, 7.18; $P = .005$), and the calcium location in the common carotid artery (OR, 6.62; $P = .006$) in comparing groups with low (0-400) and medium (400-600) calcium scores, whereas a high volume score (OR, .01; $P = .003$) alone was a significant independent determinant in the comparison between groups with high (600-1000) and medium calcium scores. *Conclusions:* Symptomatic rates of carotid plaque calcification were demonstrated to show double peaks with increasing calcium score and represent different features. Assessment of the 2 calcium-score parts might be helpful for appropriate comprehension of symptomatology and the complex

From the *Department of Neurosurgery, Nagoya City University Graduate School of Medical Sciences, Nagoya; and †Department of Medical informatics & Integrative Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

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Address correspondence to Hiroyuki Katano, MD, PhD, Department of Neurosurgery, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. E-mail: katano@med.nagoya-cu.ac.jp.

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process of carotid plaque calcification. We report a hypothesis for the mechanisms of the 2 different sections. **Key Words:** Carotid stenosis—carotid plaque—calcification—calcium score—volume score—Hounsfield value.

Coronary artery calcification is considered to be one of the important factors of vulnerable plaques along with such features as large lipid core, intraplaque hemorrhage, and a thin fibrin cap.[1] Many investigators have reported relationships between volume, weight, or percentage of calcification in coronary plaque and clinical symptoms compatible with acute coronary syndrome.[2,3] Calcium scores of coronary artery and coronary artery disease were significantly higher in patients with cardiovascular events.[4] Moderate-to-extensive coronary artery calcium was associated with an increased occurrence of ischemic stroke.[5]

On the other hand, calcification in carotid plaque has been reported as a stable factor although coronary and carotid arteries generally share common risk factors.[6] A systematic review reported that clinically symptomatic plaques have a lower degree of calcification than asymptomatic plaques.[2] Nandalur et al[7] reported that plaque calcification more than 45% of the total volume was significantly inversely associated with the occurrence of symptoms. Intrinsically, calcification has been thought to be a terminal state of the tissue in the pathologic course of atherosclerosis ending in necrosis or apoptosis. Apoptotic bodies derived from vascular smooth muscle cells have been reported to serve as a nidus for calcification.[8] Ewence et al[9] demonstrated that inflammation by calcium phosphate crystals induced apoptosis in vascular smooth muscle cells. Wu et al[10] listed other possibilities for the mechanism of vascular calcification, such as failed anticalcific processes, induction of osteochondrogenesis, abnormal Ca/Pi homeostasis, circulating calciprotein particles, and matrix degradation/modification. Nevertheless, the precise mechanisms of vascular calcification and its clinical significance including the difference in outcomes between coronary and carotid arteries have not been completely elucidated yet.

We have advocated evaluating the carotid plaque calcification by the calcium score with the hope that it may be clinically important and useful to know not only the volume of the calcification but also the hardness expressed by Hounsfield values for preoperative assessment especially considering the expansion of stents in the choice of treatments for carotid stenosis.[11,12] In this study, we used the calcium score to analyze carotid plaque calcification, focusing on its relationship with symptoms. We also discuss the difference in transitional patterns and clinical outcomes in the present findings compared with previous reports regarding calcified coronary plaques.

Patients and Methods

Patient Population and Surgical Treatments

A total of 388 carotid arteries were analyzed from 194 consecutive patients undergoing surgical treatments of carotid stenosis (carotid endarterectomy [CEA]:carotid artery stenting [CAS] = 102:92) from February 2005 to July 2014. Ten patients with occlusion of the internal carotid artery (ICA), 18 with redundant counting for bilateral treatment, 26 carotids with retreatment for restenosis, 1 case of CEA for removal of stent, and 1 case without computed tomography (CT) angiography for renal malfunction were excluded. Finally, 330 carotid arteries were enrolled in the study. Carotid arteries with stenoses were defined as "symptomatic" (n = 130) if patients had transient or permanent focal neurologic symptoms of the contralateral limbs or ipsilateral retina, whereas other carotids that did not match the previously mentioned criteria were considered "asymptomatic" (n = 200). Data for the patients are summarized in Table 1. Symptomatic carotid arteries were all treated by either CEA or CAS, whereas 24.5% of asymptomatic carotid arteries underwent surgery. The degree of carotid stenosis was significantly lower in asymptomatic carotid arteries (38.6 ± 31.7% versus 79.0 ± 12.0%).

Surgical indications for the treatment of carotid stenosis adhered to the criteria of North American Symptomatic Carotid Endarterectomy Trial[13] and Asymptomatic Carotid Atherosclerosis Study.[14] Surgical methods and selection for CEA or CAS were prosecuted as described previously.[12,15] Aspirin (100 mg/day) was administered before CEA/CAS, and clopidogrel 75 mg/day or cilostazol 200 mg/day was also prescribed after CAS.

The study design was approved by the local ethical committee, and the ethics guidelines for clinical studies of the Japanese Health, Labor and Welfare Ministry (2008) were strictly observed.

Assessment of Calcification with Multidetector Row CT Angiography

Multidetector computed tomography (MDCT) angiography was performed preoperatively in all enrolled patients with a 64- (SOMATOM Definition; Siemens Medical Solutions, Forchheim, Germany) or 16-detector row CT scanner (IDT-16; Philips Medical Systems, Best, Netherlands) as described previously.[11] The imaging acquisition parameters were as follows: spiral mode .33-second gantry rotation; collimation, 32 × .6 mm; pitch