The Use of Contrast-enhanced Ultrasonography for Imaging of Carotid Atherosclerotic Plaques

Current Evidence, Future Directions

Sandeep A. Saha, MD*, Venu Gourineni, MD,
Steven B. Feinstein, MD, FESC

KEYWORDS

• Echo-contrast agents • Microbubbles • Carotid endarterectomy • Plaque neovascularization
• Plaque neoangiogenesis • Contrast enhancement • Safety

KEY POINTS

- Current treatment guidelines recommend treatment of symptomatic patients with carotid stenosis with low or average surgical risk based on occurrence of symptoms and the degree of ipsilateral carotid stenosis. Data related to the optimal management of asymptomatic patients or those with moderate carotid stenosis (50%–69% by duplex ultrasonography) remain limited.
- Contrast-enhanced ultrasonography (CEUS) imaging of carotid arteries provides an accurate quantification of stenosis, and permits novel, real-time access to intraplaque neovascularization (IPN); a distinct marker of plaque vulnerability notwithstanding the presence of stenosis.
- IPN correlates with localized intraplaque inflammation presaging a higher risk of plaque hemorrhage and rupture.
- Two-dimensional CEUS imaging of IPN has been shown to directly correlate with the extent of neovascularization observed in histopathologic examinations of surgically excised carotid plaques.
- Detection of IPN using CEUS carotid artery imaging may be predictive of adverse cardiovascular events in patients with known coronary artery disease. If confirmed in larger clinical trials, CEUS carotid imaging may be useful for cardiovascular risk stratification by providing a marker of subclinical atherosclerosis.

INTRODUCTION

Carotid atherosclerotic disease leading to carotid stenosis is an important cause of ischemic strokes. Pivotal clinical trials performed in the United States (NASCET [North American Symptomatic Carotid Endarterectomy Trial])[1] and Europe (ESCT [European Carotid Surgery Trial])[2] provided a clear correlation between the degree of carotid stenosis and the risk of stroke in symptomatic patients. Current treatment guidelines in the United States advocate treatment with carotid endarterectomy (CEA) for symptomatic patients (defined as those who have a transient ischemic

Financial disclosures: S.A. Saha, V. Gourineni, none. S.B. Feinstein, research support from GE Life Sciences (11111606) (IIT grant) and consultant for GE Healthcare.
Division of Cardiology, Department of Medicine, Rush University Medical Center, Chicago, IL, USA
* Corresponding author. Rush University Medical Center, Division of Cardiology, 1717 West Congress Parkway, Kellogg 321, Chicago, IL 60612.
E-mail address: sandeep_a_saha@rush.edu

Neuroimag Clin N Am 26 (2016) 81–96
http://dx.doi.org/10.1016/j.nic.2015.09.007
1052-5149/16/$ – see front matter

attack [TIA] or a nondisabling stroke) considered as low or average surgical risk with ipsilateral carotid stenosis of greater than or equal to 70% on noninvasive imaging or greater than or equal to 50% by angiography with the caveat that the preoperative risk is less than 6%. This guideline was consistent with the clinical data that recognized that symptomatic patients who underwent CEA had an incidence of stroke-free survival of 93% at 5 years.[3] However, in patients with moderate carotid stenosis (defined as 50%–69% stenosis) and asymptomatic patients with high-grade stenosis (>70%), the role of revascularization with CEA or carotid artery stunting (CAS) remains unclear. Current treatment decisions rely solely on the severity of anatomic stenosis associated with the presence or absence of neurologic symptoms. A notable pitfall of using luminal stenosis to detect the presence of carotid atherosclerosis is highlighted in (**Fig. 1**). Essentially, luminal characteristics may not fully represent the presence of a carotid plaque because of effects associated with positive arterial wall remodeling. The current guidelines also do not account for other characteristics of the atherosclerotic plaque, including presence of intraplaque neovascularization (IPN). It may now be possible to develop a more comprehensive and predictive model of plaque vulnerability by incorporating the contrast-enhanced ultrasonography (CEUS) identification of IPN coupled with preexisting anatomic descriptors of stenosis. Thus, the addition of CEUS may afford an opportunity to provide a risk assessment beyond the standards of luminal stenosis, especially in asymptomatic patients and in symptomatic patients with lower degrees of carotid stenosis.

Unenhanced duplex ultrasonography remains the principal modality for diagnosing and monitoring the progression of carotid artery stenosis. In general, diagnosticians rely on the NASCET criteria[1] to estimate the degree of stenosis within the internal carotid artery based on blood flow velocity measurements using Doppler ultrasonography. However, substantial errors limit the success of Doppler imaging technology and include individual variation in vascular anatomy, body habitus, or vessel wall calcification. Optimal two-dimensional (2D) ultrasonography imaging of carotid plaques requires controlling for tangential imaging planes caused by variations in carotid artery anatomy, and as such depends on the operator's skill. The quality of the examination is also reliant on the sonographer's ability to ensure that serially acquired carotid luminal surfaces remain within the image plane. In addition, Doppler flow measurements are angle dependent, and misalignment may lead to significant error in estimating the severity of luminal stenosis using the NASCET criteria. Comparative noninvasive imaging modalities used for carotid artery imaging include magnetic resonance (MR) imaging, computed tomography (CT), and PET/CT imaging. These related modalities provide an assessment of carotid artery stenosis albeit at increased costs, exposure to ionizing radiation, and prolonged image acquisition and processing times. Three-dimensional (3D) carotid ultrasonography imaging may circumvent the associated limitations of 2D ultrasonography, as is more fully discussed elsewhere in this issue. In a comparison of multiple imaging modalities for preoperative imaging in patients with carotid stenosis, Pfister and colleagues[4] noted that contrast-enhanced 3D B-flow ultrasonography had the highest correlation with surgical evaluation of internal carotid artery stenosis, with a Spearman correlation coefficient of 0.93. There are no reported studies to date using 3D CEUS imaging of carotid IPN. Importantly, only CEUS can directly image the IPN in real time and at the bedside. Overall, ultrasonography and CEUS provide a readily accessible imaging strategy for rapid assessment of carotid atherosclerotic disease.

Gas-filled microbubbles serve as excellent intravascular ultrasonography contrast agents based

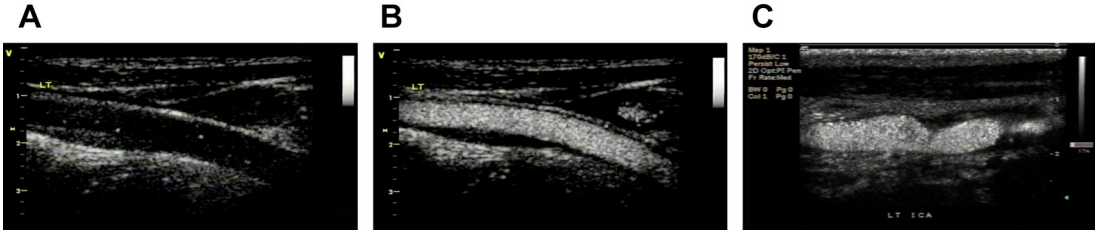

Fig. 1. Contrast-enhanced ultrasonography (CEUS) detection of carotid atherosclerotic plaques. (*A*) An unenhanced ultrasonography image of the common carotid artery, in which the plaque is faintly visible. (*B*) CEUS image of the same vessel, highlighting the presence of the plaque without significant luminal stenosis (positive remodeling). (*C*) CEUS image of the internal carotid artery showing intrusion of the vessel lumen of the plaque resulting in luminal narrowing (negative remodeling).