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VIEWPOINT

Contrast Ultrasound Imaging of the Carotid Artery Vasa Vasorum and Atherosclerotic Plaque Neovascularization

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Cardiovascular disease is associated with the aging of the population, obesity, metabolic syndrome, and diabetes. Therefore, it is important to develop non-invasive imaging systems to detect "at-risk" populations. New data suggest that contrast-enhanced ultrasound (CU) imaging of the carotid arteries enhances luminal irregularities (i.e., ulcers and plaques), improves near-wall, carotid intima-media thickness, and uniquely permits direct, real-time visualization of neovasculature of the atherosclerotic plaque and associated adventitial vasa vasorum. With continued clinical investigation, CU imaging of the carotid artery may afford an effective means to non-invasively identify atherosclerosis in "at-risk" populations while providing new standard for therapeutic monitoring. (J Am Coll Cardiol 2006;48:236–43)
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With approximately 1.2 million heart attacks and 750,000 strokes afflicting an aging American population each year, cardiovascular disease remains our country's number one cause of death. Unfortunately, this grim statistic is likely to worsen in the years ahead due to the prevalence of obesity, metabolic syndrome, and clinical diabetes in the burgeoning baby boomer population. Therefore, it is critical that we develop non-invasive screening methods that safely and reliably identify surrogate markers of atherosclerosis, indicating the presence of unstable plaques and an increased risk of cardiovascular events. Once "vulnerable patients" (1–3) are identified, it may be possible to institute timely preventive therapy, monitor its effectiveness, and potentially reverse the course of these disease processes.

New data suggest that contrast-enhanced ultrasound (CU) imaging of the carotid arteries may help identify patients who are at increased risk of cardiovascular diseases. Because CU agents are currently Food and Drug Administration-approved only for use in imaging the heart structures, their off-label use in vascular imaging requires institutional research approval. Where such approval is obtained, physicians can perform CU carotid imaging in the office or hospital setting, obtaining direct real-time carotid images with enhanced assessment of the arterial lumen and plaque morphology, improved resolution of carotid intima-media thickness (c-IMT), and, importantly, direct visualization of the adventitial vasa vasorum and plaque neovascularization (3–5). The latter is particularly significant because neovascularization of the atherosclerotic plaque is considered a predictor of vulnerable lesions in patients (6–16). Moreover, carotid atherosclerotic plaque appears to indicate the presence of systemic atherosclerosis. Therefore, with continued investigation, CU imaging of the carotid vasa vasorum promises to become a routine noninvasive means of identifying an atherosclerotic plaque in its earliest stages. These observations may lead to early clinical interventions with medical therapies (statins, anti-inflammatory medications, angiotensin-converting enzyme, or calcium-channel medications, and so on) or mechanical procedures (stents, carotid endarterectomy surgery), potentially reducing the incidence of heart attack and stroke.

UNDERSTANDING THE ROLE OF VASA VASORUM AND PLAQUE NEOVASCULARIZATION IN THE DEVELOPMENT OF ATHEROSCLEROSIS

An atherosclerotic plaque begins to develop as a result of damage/insult/hypoxia to the endothelial cells of the vascular system (5,17). As atherosclerosis progresses, reduced oxygen diffusion diminishes the nutrient supply reaching the arterial wall, resulting in hypoxia. Reactive physiologic compensation causes a thickening of the intima-media complex exceeding the oxygen diffusion threshold (250 to 500 μm), inducing ischemia, which then triggers a continual release of angiogenic growth factors (vascular endothelial growth factor, tissue hypoxic factor, and so on). It is believed that the absence of pericytes in some angiogenic vessels causes these immature vessels to "leak" potentially noxious and inflammatory plasma components (hemoglobin, oxidized low-density lipoprotein cholesterol, lipoprotein[a], glucose, advanced glycation end products, and inflammatory cells) into the extracellular matrix of the media/intima, increasing plaque volume. The ongoing deposit of plasma components appears to further reduce vessel wall oxygen diffusion, triggering continued growth of an-

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Abbreviations and Acronyms

c-IMT = carotid intima-media thickness
CU = contrast-enhanced ultrasound
MRI = magnetic resonance imaging

giogenesis. Ultimately, the plaque is enveloped in luxurious adventitial vasa vasorum and intraplaque neovascularization, a hallmark of symptomatic atherosclerosis (18).

Clinician researchers have long appreciated a relationship between the vasa vasorum and the development of atherosclerosis. For well over 100 years, pathologists have observed that the adventitial vasa vasorum serves as the primary source of the neovascular blood supply within plaque (19). At autopsy, prominent angiogenic vessels were observed within the media and intima of the arterial walls of patients with atherosclerosis. Moreover, in a pre-morbid setting, the media and intima tunica layers of the vessel walls received nominal nutrient blood supply from luminal diffusion and, to a lesser degree, from the adventitial vasa vasorum (20).

The historic work of Koster (21), Beeuwkes et al. (8), and Barger et al. (5) linked the clinical presence of angiogenic neovascular vessels to atherosclerotic plaque; as noted: "There is no doubt that these small vessels of the arterial wall exist in far greater numbers in regions associated with plaque. Observations (were) made as early as 1876 (21) and confirmed in 1938 (Winternitz)" (8). Beeuwkes et al. (8) and Barger et al. (5) used postmortem cinemicrographic techniques to demonstrate a direct anatomic connection between coronary adventitial vasa vasorum and atherosclerotic plaque. These cine films revealed arterial and venous vasa vasorum "bathing" (supplying blood to) the arterial atherosclerotic plaque in patients who suffered fatal cardiovascular events. Moreover, adventitial neovascularization and plaque neovascularization were directly linked to atherosclerosis in the seminal work of Barger et al. (5): "Hypothesis: vasa vasorum and neovascularization of human coronary arteries, a possible role in the pathophysiology of atherosclerosis." Subsequently, in 1990, Martin et al. (19) dashed the widely held belief that the luminal surface generates atherosclerosis.

More recent clinical pathologic studies by Fleiner et al. (15) demonstrated that the presence and degree of neovascularization within vulnerable plaque is associated with plaque rupture and clinical occlusive cardiovascular events. And as Kumamoto et al. (11) observed: "There was a significant positive correlation between the density of new vessels in the intima and the incidence of luminal stenosis, the extent of chronic inflammatory infiltrate, the formation of granulation tissue, or the atheromatous changes, whereas the vascular density decreased in the extensively hyalinized and calcified intima. The newly formed intimal vessels originated mainly from the adventitial vasa vasorum and also partly from the proper coronary lumen. The intimal vessels that originated from the adventitia occurred approximately 28 times more frequently than those that originated from the luminal side."

In addition, Moreno and Fuster (16) have directly linked atherosclerosis and diabetes to the formation of vulnerable plaque. Recently, Mauriello et al. (22) examined 544 coronary segments in 16 patients who experienced fatal coronary events. The results revealed the presence of diffuse, active inflammation in the entire coronary vascular system, in patients with both stable and vulnerable plaques.

Using animal models with dietary-induced atherosclerosis, Williams et al. (23) showed regression of intima and media neovascularization after a reduction of cholesterol feeding. In addition, Wilson et al. (24) used microcomputed tomography techniques to observe the induction of coronary adventitial vasa vasorum in the pig and, subsequently, regression after statin therapy. Importantly, the authors noted that the excessive growth of adventitial vasa vasorum preceded the development of luminal plaques. Similarly, Moulton et al. (25) studied antiangiogenesis therapies in an experimental animal model of atherosclerosis.

CU CAROTID IMAGING FOR IDENTIFICATION OF SURROGATE MARKERS OF ATHEROSCLEROSIS

Recent studies indicate that CU carotid imaging can be clinically useful in identifying surrogate markers of atherosclerosis (3,26–28). These studies primarily focus on three areas of clinical importance:

1) enhancement of the carotid lumen and plaque morphology;
2) improved resolution of the c-IMT of both the near and far walls; and
3) identification of atherosclerotic-related neovascular changes within the adventitial vasa vasorum and plaques.

The CU carotid studies of the lumen often reveal previously undetected irregularities, such as plaques and ulcers (Fig. 1). Sirlin et al. (29) were the first to use CU agents to identify the lumen in a series of in vitro and preclinical studies. Their subsequent clinical validation study in 14 patients revealed an excellent correlation of the CU images with the results of cerebral angiograms (30). Our laboratory has reported additional data suggesting the clinical utility of CU agents for carotid lumen enhancement (26). If confirmed in larger clinical trials using other modalities (computerized tomography angiography and magnetic resonance imaging [MRI]), CU carotid lumen imaging may reduce the need for additional invasive diagnostic procedures, in essence serving as a noninvasive angiogram.

The CU carotid studies also enhance visualization of the c-IMT, which has served as a surrogate marker of atherosclerosis since Pignoli and Longo (31) first reported their work in 1986. Numerous additional clinical trials have validated c-IMT as a reliable surrogate marker of atherosclerosis. However, without contrast, c-IMT measurements were ineffective in approximately 7% to 27% of studies due

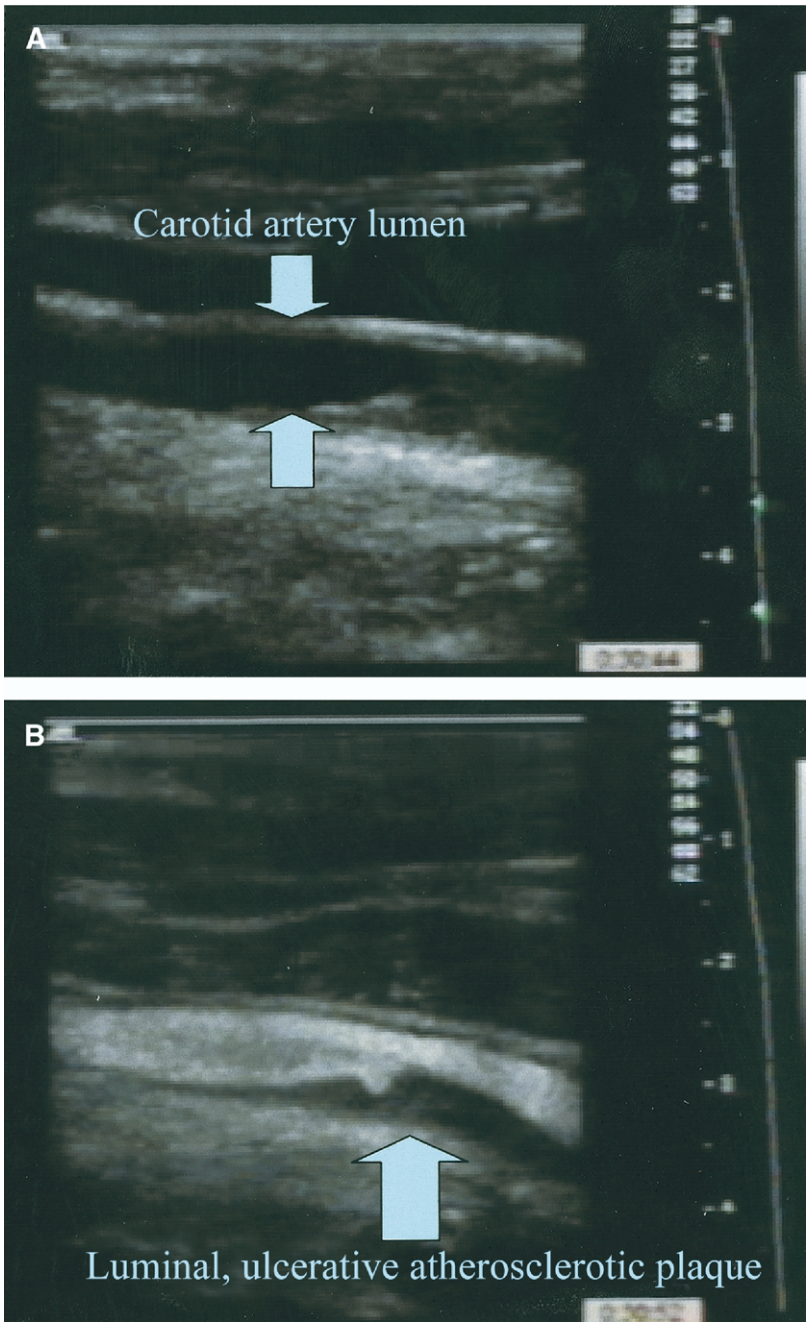

Figure 1. **(A)** This image is an example of an unenhanced carotid artery ultrasound image. **(B)** After an intravenous injection of an ultrasound contrast agent, the carotid artery lumen appears echodense **(white)** revealing an ulcerative plaque along the far wall. The presence of the ulcer was not clearly defined in the previous unenhanced ultrasound examination.

to the technical difficulties in reliably imaging the anterior wall of the carotid artery (32). For example, in 1998, van Swijndregt (32) reported that the near wall of the carotid vessel was not reliably identified in vitro using extravascular ultrasound techniques. Moreover, in vitro measurement of c-IMT of the non-enhanced near wall was described as fraught with error due to inherent acoustic properties of overlying soft tissues; in these studies, the authors compared extravascular ultrasound images with tissue histology and intravascular ultrasound images (32). In addition, Wong et al. (33) reported that conventional ultrasound, without contrast, routinely underestimated near wall c-IMT thickness by 20%. In 2003, we described the clinical use of CU agents to enhance carotid images and improve the definition of the carotid near wall and associated near wall c-IMT (34). Our laboratory demonstrated two distinct advantages of imaging the carotid near wall versus the far wall: first, the near wall c-IMT is thicker than the far wall, particularly when the lumen is enhanced with ultrasound contrast agents, and, second, the progression rate of atherosclerosis is increased in the near wall versus the far wall. This finding has been noted by Meyer et al. (unpublished data, 1996).

Notably, the variability of atherosclerosis within the vascular arterial system was described by Bots et al. (35). Moreover, as Hodis et al. (36,37) demonstrated, the thicker the c-IMT, the more notable the regression after statin therapy. Therefore, while validation is required, the improved visualization of the near wall may serve as an additional surrogate marker for atherosclerosis and, consequently, contribute to the clinical assessment atherosclerosis therapy (26).

Figure 2 illustrates CU visualization of the carotid artery lumen and the anterior aspect of the c-IMT, thus permitting more precise measurements.

Using CU to delineate carotid adventitial vasa vasorum, our initial studies demonstrate that arterial nutrient flow predominately emanates from the vasa vasorum, generating neovascularization within the media and intima layers of atherosclerotic plaque (Fig. 3). These observations provide a clinical link between earlier pathologic studies and clinical medicine, and support the theory that atherosclerosis develops "outside in" rather than "inside out." Figure 4 shows how CU can be used to identify neovascularization, revealing angiogenesis within a carotid artery plaque in a patient with cerebral transient ischemia. Due to the presence of a significant carotid stenosis associated with cerebral vascular symptoms, the patient underwent a surgical carotid endarterectomy. Figure 5 reveals the presence and marked degree of neovascularization within an unstable carotid artery plaque; the presence of neovascular vessels was highlighted using CD-31 stain.

Our CU carotid imaging results are consistent with MRI studies that identified and characterized intraplaque neovascularization (38,39). Recently, Kerwin et al. (40) used MRI to demonstrate the presence and degree of carotid plaque neovascularization, while Takaya et al. (41) used serial MRI studies to demonstrate that intraplaque hemorrhage may lead to the enlargement of a carotid artery plaque. Additionally, in a recent report by Magnoli et al. (28), the authors correlated the width of adventitial vasa vasorum to c-IMT using contrast-enhanced, B-flow imaging in pa-

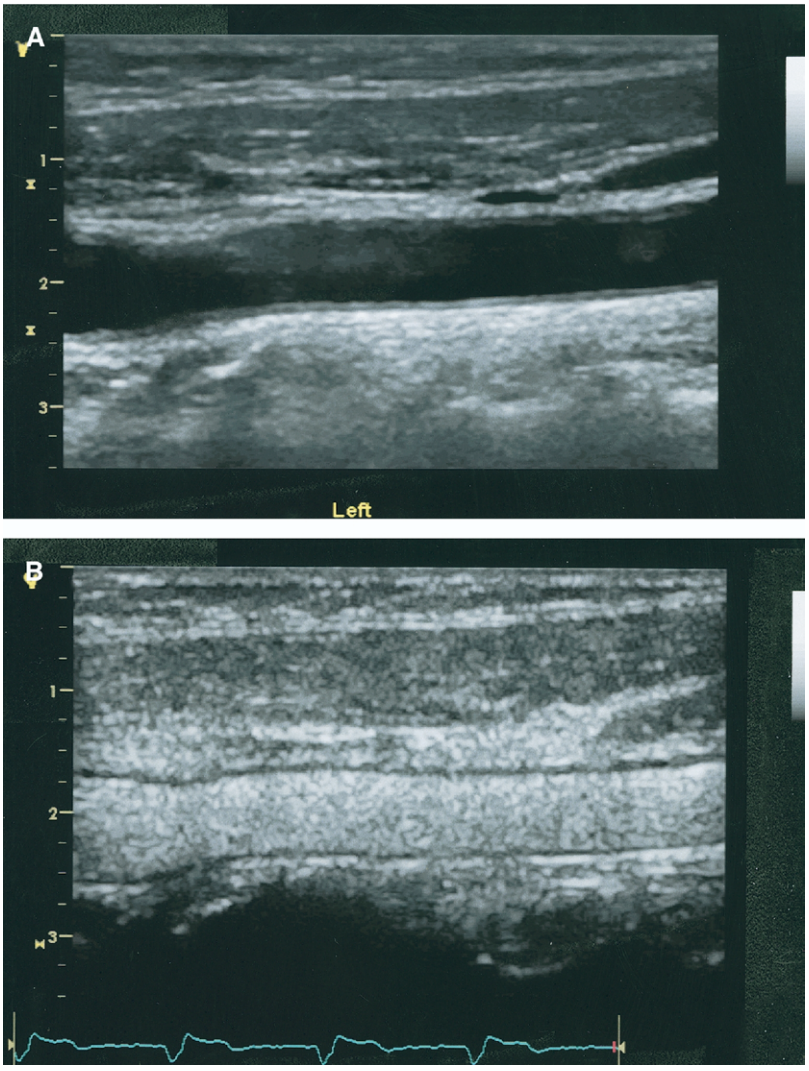

Figure 2. **(A)** The carotid intima-media thickness of the near wall of the carotid artery is not well visualized, limiting measurement. **(B)** After an intravenous injection of an ultrasound contrast agent, the near-wall carotid intima-media thickness is identified, permitting measurement of the carotid intima-media thickness.

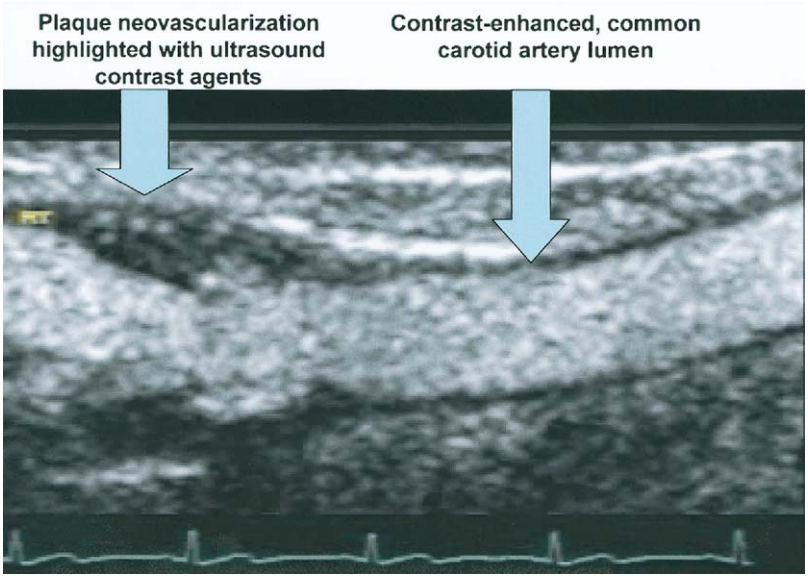

Figure 3. Ultrasound contrast agents enhance the vessel lumen and reveal the presence of intraplaque angiogenesis, emanating from the adventitial vasa vasorum.

tients with known coronary artery disease. In their report, the authors commented that only after the administration of intravenous contrast agents were the adventitial vasa vasorum identified with B-flow imaging. In the control population (no coronary artery disease), the administration CU agents did not enhance the vasa vasorum. This represents the first reported effort to use CU to quantify the degree of neovascularization in patients with atherosclerosis.

CU CAROTID IMAGING FOR IDENTIFICATION OF REGRESSION OF ADVENTITIAL VASA VASORUM

Contrast-enhanced ultrasound carotid imaging recently allowed us to observe regression of adventitial vasa vasorum associated with atherosclerotic plaque neovascularization in a 53-year-old patient with a history of diabetes. A CU carotid examination, performed as part of a cardiovascular prevention screening, revealed distinctly prominent vasa vasorum (Fig. 6). Despite his diabetes, the patient was not on statin therapy at the time of the initial examination but subsequently was placed on a daily statin dose. Eight months later, a follow-up CU carotid examination revealed a marked decrease in the adventitial vasa vasorum (Fig. 7). While it is premature to conclude that CU imaging can reliably identify progression and regression of atherosclerosis in patients, it is nevertheless intriguing to note that these observations are consistent with experimental findings reported by Heistad and

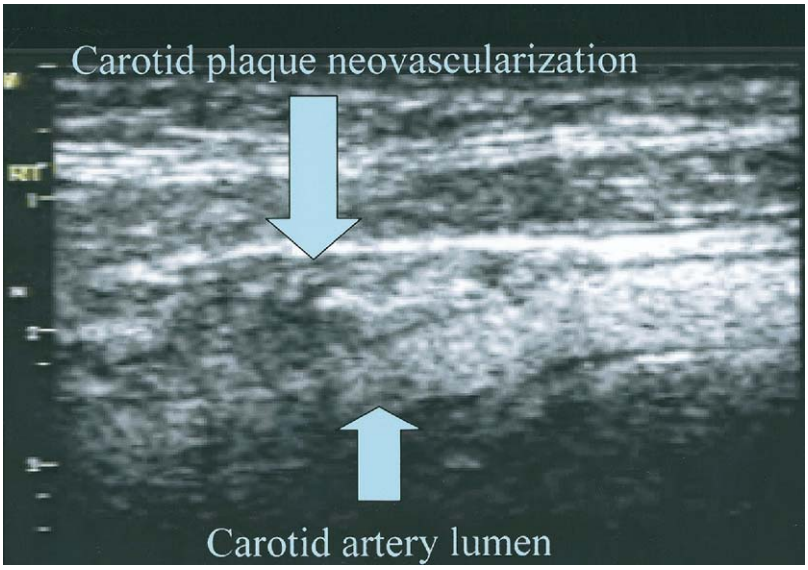

Figure 4. The presence of intraplaque angiogenesis is highlighted by the use of ultrasound contrast agents. The image was obtained during an ultrasound examination of a patient who had a history of a transient ischemic attack.

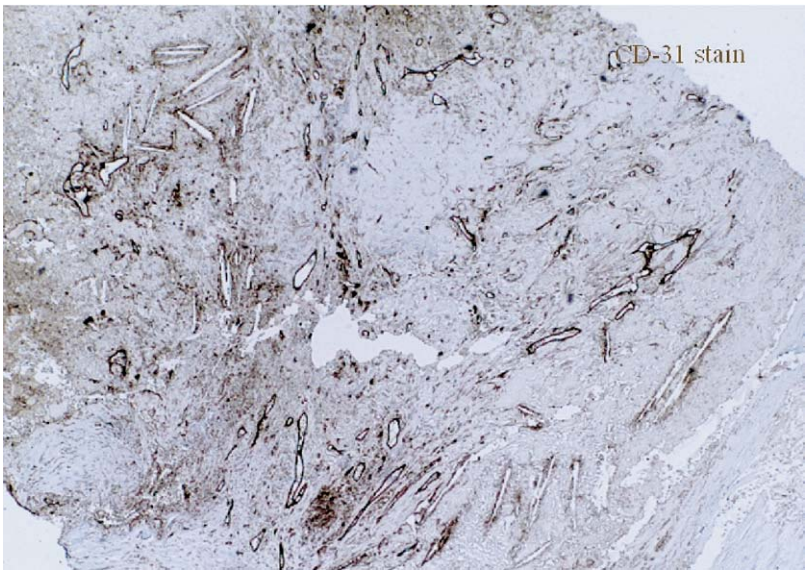

Figure 5. This photomicrograph highlights the abundance of vascular endothelial cells identified within the carotid artery plaque (Fig. 4). This specimen was obtained at the time of carotid artery endarterectomy surgery and was prepared with a CD-31 stain.

Armstrong (42), Wilson et al. (24), Moulton (43), and Williams et al. (23) describing the induction and subsequent regression of the vasa vasorum.

NEOVASCULAR NOURISHMENT OF TUMORS

Contrast-enhanced ultrasound carotid imaging may be useful in assessing excessive neovascularization in cancerous tumors, which resemble atherosclerotic plaques because both tumor growth and atherosclerotic plaque growth are supported by angiogenesis generated in connection with local and systemic growth factors. Folkman (6) first described the association between angiogenesis and tumors in 1971, contributing to the growing body of literature linking neovascularization to atherosclerosis. Similarly, in 2001, Ross et al. (44) proposed that angiogenesis stimulators are associated with atherosclerosis tumor growth. These path-breaking studies suggest an expanded paradigm focusing on the role of angiogenesis in the development of atherosclerosis.

CONCLUSIONS

Our contrast carotid imaging studies appear to support Gardin's (45) view that vascular imaging represents the next frontier for cardiologists. Because CU agents are safe, commercially available, and approved for use in cardiac

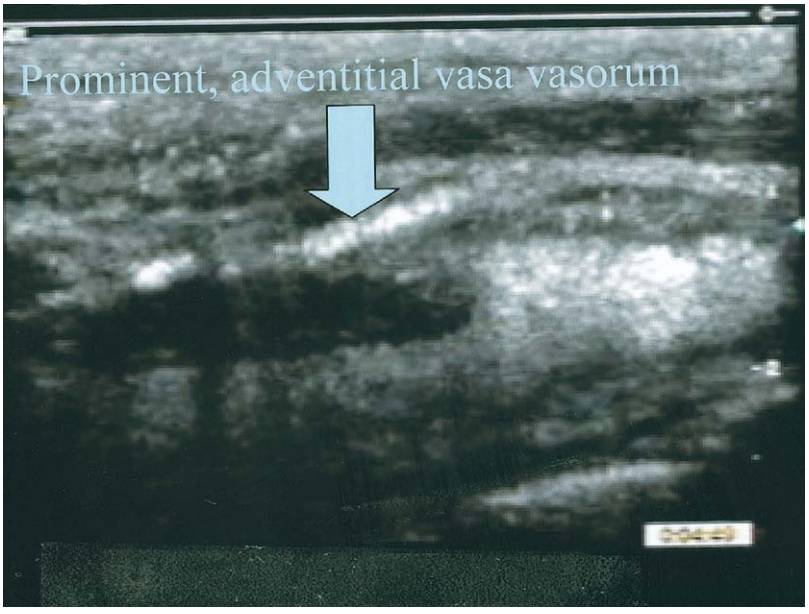

Figure 6. A prominent blood vessel (adventitial vasa vasorum) is readily identified along the near wall of the carotid artery in this 53-year-old man with diabetes. Of note, at the time of these studies, the patient was not on statin therapy.

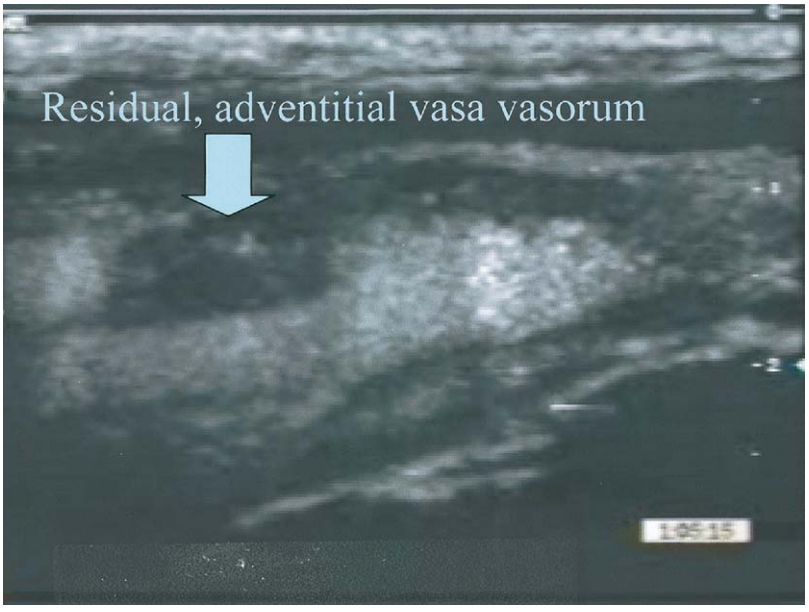

Figure 7. After 8 months of statin therapy, the patient (Fig. 6) returned for a follow-up contrast-enhanced carotid ultrasound examination. Note that the adventitial vasa vasorum vessel prominently seen in Figure 6 has been significantly reduced. This may represent regression of the adventitial vasa vasorum after antiangiogenesis therapy with statins.

imaging, physicians today can perform clinical carotid CU imaging as a research application. In patients at risk for developing symptomatic atherosclerosis, CU carotid examinations may help identify and quantify the presence and degree of neovascularization of the vasa vasorum and arterial plaque, permitting a more reliable assessment of cardiovascular risk. With continued investigation, CU vascular studies may be routinely performed at the patient's bedside or in an outpatient setting, using portable and economical ultrasound equipment (46). Medicare reimbursement codes currently include the use of ultrasound contrast agents for enhancement of cardiac chambers, based upon a recommendation from the American Society of Echocardiography in 2000 (47); a similar Medicare reimbursement code could follow for contrast-enhanced vascular ultrasound applications. Of interest, all comparable non-invasive imaging techniques (computed tomography, MRI, and nuclear) use enhancement agents for delineation of anatomy and organ perfusion.

Thus, CU carotid imaging may become an indispensable method of identifying atherosclerosis in its earliest stages, thereby facilitating early intervention and ultimately reducing the incidence of heart attack and stroke. In addition, in the future, CU technology may be used to help monitor futuristic ultrasound-based therapies including ultrasound-directed, site-specific delivery systems for antiangiogenic agents (3). This could permit the targeting of organ systems with antiangiogenic agents and therapies for treatment of vulnerable plaque.

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