

EDITORIAL COMMENT

Stroke: Cause and Effect—Seek and Ye Shall Find*

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There is increasing evidence that carotid plaque morphology plays a significant role in the generation of cerebral ischemic symptoms in addition to—and potentially independent from—carotid artery stenosis. Imaging techniques that have the ability to characterize atheromatous plaque noninvasively may therefore be used to identify vessel wall disease that is associated with clinical events. Magnetic resonance imaging (MRI) is emerging as one such noninvasive imaging tool that is able to distinguish different plaque constituents.

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When vessel wall MRI is coupled with the proven benefit of brain MRI to identify acute ischemic brain lesions, this technique provides a single imaging modality for comprehensive carotid-cerebral imaging not provided by computed tomography (CT) or ultrasound, which are both commonly used imaging techniques for the carotid artery and brain. The feasibility of imaging the causative carotid artery lesion and end-organ brain injury in patients with acute stroke has been further enhanced by the application of high-field (3-T) MRI scanners. 3-T MRIs for brain and carotid assessment exploit the increased signal-to-noise ratio generated at this field strength, which can be translated into improved spatial or temporal resolution. Previous work by Kerwin et al. (1) has shown the feasibility of applying similar proven

techniques used at the lower field strength of 1.5-T at this higher level, and 3-T imaging of the carotid arteries is becoming the method of choice for high-resolution vessel wall imaging.

Similarly, MRI has a distinct advantage over alternative techniques for imaging the brain in hyperacute stroke because it allows identification of acute cerebral infarction using diffusion-weighted imaging within a very short time (minutes) of the cerebral insult. It is therefore possible to use an MRI to definitively diagnose acute cerebral infarction overcoming the known limitation of relying on clinical diagnosis of stroke (2).

Two papers in this issue of *iJACC* have applied 3-T MRI carotid and brain imaging to diagnose cerebral infarction and to better understand the underlying cause. Freilinger et al. (3) used 3-T imaging to assess patients with imaging evidence of acute cerebral infarction but with no obvious underlying cause (e.g., cryptogenic stroke). Patients underwent extensive investigation to exclude a cardiogenic source of thromboemboli or emboli arising from the proximal thoracic aorta; patients also had no significant carotid stenosis, at least not greater than 50% according to NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria. Lindsay et al. (4) undertook a similar combined approach of brain and carotid imaging at 3-T in the acute phase of MRI-proven cerebral infarction. Although not restricted to a specific level of carotid stenosis, the majority of cases were found to be <70%.

Freilinger et al. (3) assessed carotid plaque for the presence of American Heart Association (AHA) type VI plaque defined according to intraplaque hemorrhage (IPH), surface thrombus, or cap rupture, all thought to play a significant role in the generation of neurological symptoms by artery-to-artery embolization. Lindsay et al. (4) studied these individual characteristics in more depth and compared the prevalence

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of IPH, cap rupture, and surface thrombus with an age- and sex-matched asymptomatic control group who were also matched for degree of carotid stenosis. Both studies demonstrated that AHA type VI plaque was significantly more common ipsilateral to the index cerebral infarct compared with either a control asymptomatic group or the patients' contralateral asymptomatic carotid artery.

In addition to the use of combined carotid/brain imaging and the use of 3-T MRI, used in both these studies, each report offers new information regarding the acute phase of stroke and its underlying etiology. As noted by Freilinger et al. (3), cryptogenic stroke, defined according to current methods, comprises a significant proportion of strokes, which has the potential to leave patients underdiagnosed. This limited information, arising from the lack of diagnosis of an underlying cause for their stroke, will result in suboptimal secondary prevention. Even in patients with <50% stenosis, the prevalence of type VI plaque was found to be 37.5%, providing evidence of an otherwise hidden but potentially treatable source of future ischemic cerebral events.

Analysis of plaque morphology by Lindsay et al. (4) demonstrated that characteristics (e.g., plaque rupture) within AHA type VI plaque may have greater down-stream end-organ effects as evidenced by greater acute cerebral infarct volume. This volume will depend on a number of factors, including embolic load from the causative carotid lesion and how proximal the emboli impact within the cerebral circulation. Large areas of plaque ulceration might be expected to deliver larger thromboemboli compared with minor plaque surface disruption or endothelial activation. The demonstration of fewer lesions and decreased infarct volume with IPH suggests this might act as a useful harbinger of future events before significant brain damage.

The demonstration of complicated AHA type VI plaque in symptomatic but not severely stenotic carotid disease is not new (5), nor is the demonstration

of a higher prevalence of complicated plaque associated with cerebral symptoms (6). Parmar et al. (7) recently demonstrated the association of AHA type VI plaque with transient ischemic stroke and stroke in the acute setting. Lindsay et al. (4), however, have also shown the specific role of carotid plaque rupture in brain infarct generation. The demonstration of only partial healing of this plaque feature on follow-up imaging also suggests this represents an ongoing source for thromboemboli and a potential therapeutic target for secondary prevention. These unhealed lesions are presumably similar to those identified by Takaya et al. (8), who found these lesions to be at risk of causing events over a 2-year follow-up period in an asymptomatic population.

The demonstration of complicated carotid atheroma in nonstenosing (<50%) vessel wall disease as shown by Freilinger et al. (3) is supported by a number of recent studies (9,10). It is becoming clear that minimal carotid disease (as little as 2 mm in thickness) may contain areas of advanced atherosclerosis, which, despite its size, is presumably still prone to causing thromboembolism. The realization that even apparently "minor" atherosclerosis may harbor high-risk disease should change our perception of what constitutes risk for a patient.

The imaging tools (multimodal MRI) are now available to identify arteries, and thus patients, at increased risk. This patient population (i.e., stroke patients) is self-selecting and is already likely undergoing brain, and potentially carotid, MRI. Vessel wall characterization is therefore a practical addition to routine imaging assessment of these patients. However, while seeking and finding is the first step, knowing what to do with the information is a whole other question.

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