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EDITORIAL COMMENT

Atherosclerotic Plaque, Adventitia, Perivascular Fat, and Carotid Imaging*

Erling Falk, MD, PHD,† Troels Thim, MD,† Ingrid Bayer Kristensen, MD‡
Aarhus, Denmark

The arterial adventitia undergoes remodeling in response to a variety of arterial injuries (1). In restenosis after balloon angioplasty, adventitial fibrosis, thickening, and shrinkage are common and contribute to constrictive remodeling and luminal narrowing (2–4). In atherosclerosis, adventitial inflammation and increased vascularization via vasa vasorum (angiogenesis) are common, particularly in advanced plaques that are considered vulnerable to rupture and thrombosis (5,6). Whether adventitia also thickens in atherosclerosis as it does in restenosis is less well documented but suggested by Skilton et al. (7) in this issue of *iJACC*.

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Skilton et al. (7) describe a noninvasive method they think could be useful in the assessment of adventitial thickening in atherosclerosis. By the use of ultrasound, they measured the carotid extra-media thickness (EMT), defined as "the distance between the carotid media-adventitia interface and the jugular lumen," where the distance is smallest and readily imaged (approximately 1 to 1.5 cm proximal to the carotid bulb). This measure includes the venous wall, perivascular adipose tissue, the arterial adventitia, and an unknown extent of the carotid tunica media next to adventitia (in the near wall of the carotid artery, the true adventitia-media transition is hidden in the echo produced by adventitia) (8), but the authors claim that carotid EMT consists predominantly of the arterial adventitia and can be used to assess its thickness.

Carotid EMT is distinct from carotid intima-media thickness (IMT) that was measured just proximal to the carotid bulb. Carotid EMT was 0.737 ± 0.112 mm (mean ± SD) with no more than 0.1 mm difference between groups, a difference that corresponds to the mean diameter of a single adipocyte (9). Carotid EMT and IMT correlated with each other and with cardiovascular risk factors. In multiple regression analysis, diabetes, high-density lipoprotein-cholesterol and systolic blood pressure predicted EMT independently of IMT. No prognostic information is reported, but the authors suggest that measurement of EMT in addition to IMT might provide a more complete assessment of the vascular changes associated with cardiovascular risk factors (7).

What is Carotid EMT?

Carotid EMT consists of the venous wall, perivascular adipose tissue, the arterial adventitia, and part of the arterial media, but ultrasound is not able to distinguish between these components and determine their relative contribution to EMT. To find out, we went to the autopsy room, removed a few carotid arteries with surrounding tissues, cross-sectioned the specimens at approximately 6-mm intervals, and studied the region of interest (Figs. 1 to 3). Although the border between the arterial adventitia and the periadventitial tissues was difficult to define exactly, the carotid EMT consisted of a significant amount of adipose tissue either within or around adventitia, particularly in the subject who was obese (Figs. 2 and 3). On the basis of these observations, it is quite plausible that the amount of perivascular adipose tissue rather than adventitial thickening

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From the †Institute of Clinical Medicine and ‡Institute of Forensic Medicine, Faculty of Health Sciences, University of Aarhus, Aarhus, Denmark.

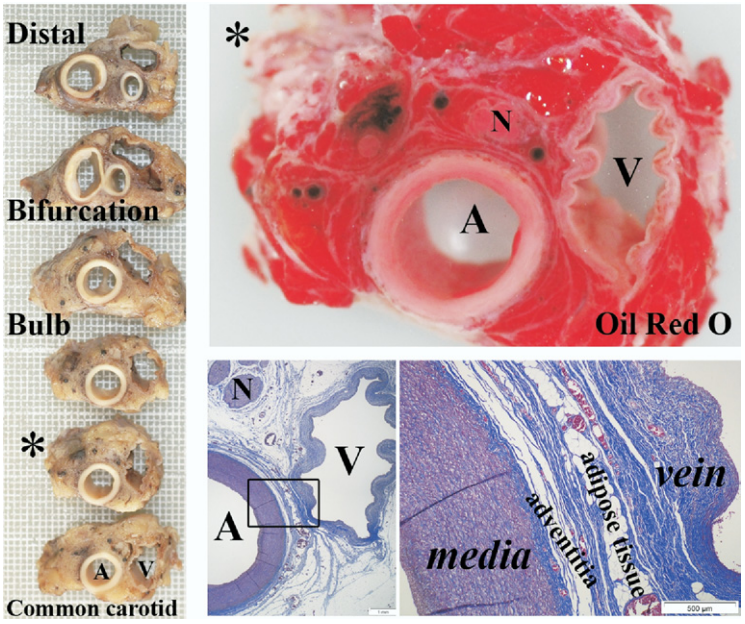

Figure 1. Carotid Artery, Jugular Vein, and Fat

Common carotid artery and its bifurcation with surrounding tissues were cross-sectioned at approximately 6-mm intervals and photographed with the proximal surface up **(left)**. The segment containing the region of interest (*, where extra-media thickness was measured by ultrasound) was stained macroscopically with Oil Red O (**top right**; lipid is **red**) and microscopically with trichrome for connective tissue (**bottom right**; collagen, including adventitia, is **blue**). Adipose tissue is observed between the common carotid artery (A) and the jugular vein (V) both macroscopically and microscopically. N = vagus nerve.

explains the results reported by Skilton et al. (7). If so, there may be an easier way to get the additional information obtained by measuring carotid EMT by ultrasound.

Periarterial Fat and Neck Circumference

Perivascular fat is distributed widely throughout the vasculature, and the amount increases with inactivity and excess calorie intake (10). The adipose tissue surrounding arteries can express proinflammatory and vasoactive adipocytokines that may contribute both to insulin resistance and to macrovascular disease (10). It was recently suggested that visceral fat, measured as waist and perhaps neck circumference, might provide an easily measured index of the body's periarterial and periarteriolar fat (10), and the amount of fat around the brachial artery, determined by high-resolution magnetic resonance imaging, was found to correlate positively with visceral adiposity and negatively with insulin sensitivity (11).

In the study by Skilton et al. (7), components related to the metabolic syndrome (diabetes, high-density lipoprotein cholesterol, and systolic blood pressure) were the strongest predictors of carotid EMT in multivariate regression models. Age- and sex-adjusted obesity, body mass index (BMI), and waist circumference also predicted carotid EMT, but BMI lost significance in the multivariate models, and waist circumference was not included because of incomplete data. Neck circumference was not measured but is known to correlate strongly with obesity, BMI, waist circumference, waist-to-hip ratio, insulin resistance-related factors, and cardiovascular risk factors (12,13). In fact, when Vague (14) more than 50 years ago described fat distribution as an important obesity-related risk factor for diabetes and atherosclerosis, he used a neck skinfold to assess upper-body fat distribution. Neck adiposity is easy to assess by measuring neck circumference with a tape measure, and its relationship to carotid EMT measured by ultrasound deserves to be clarified by those who consider to explore the incremental predictive value of carotid EMT in cardiovascular risk assessment.

The considerations discussed in the previous paragraphs extend to other imaging modalities. Like carotid EMT measured with ultrasound, carotid ^{18}F-fluorodeoxyglucose (FDG) uptake

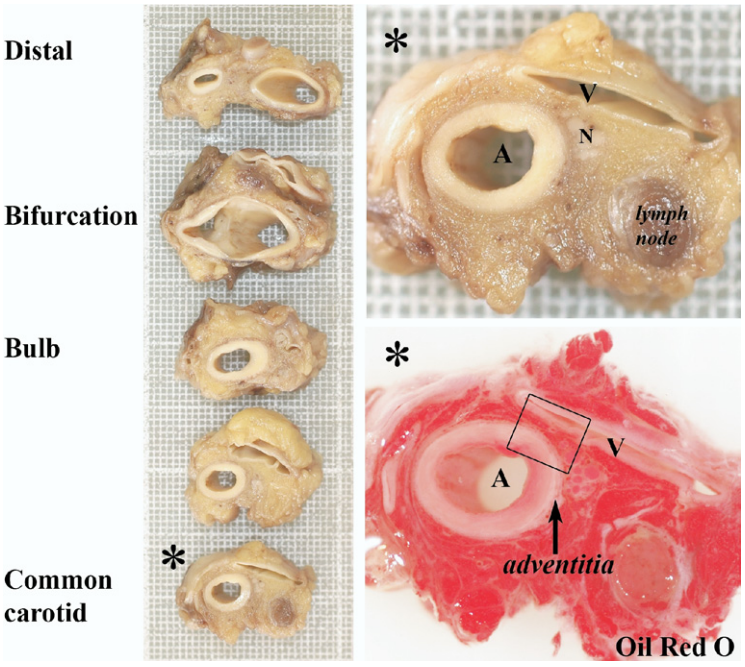

Figure 2. Carotid Artery, Jugular Vein, and Fat Accumulation

Common carotid artery and its bifurcation with surrounding tissues from an obese person (BMI 30 kg/m^2) were cross-sectioned at approximately 6-mm intervals and photographed with the proximal surface up **(left)**. The segment containing the region of interest (*, where EMT was measured by ultrasound) was stained macroscopically with Oil Red O, showing abundant red-stained adipose tissue between adventitia of the common carotid artery (A) and the jugular vein (V). The individual tissue components contributing to EMT were identified by microscopic examination (Fig. 3, area within square). EMT = extra-media thickness; N = vagus nerve.

detected by positron emission tomography correlates strongly with the metabolic syndrome, including the waist circumference (15,16). The FDG uptake is presumed to reflect inflammation within the atherosclerotic lesion (17), but this signal also may be confounded by obesity-related changes outside the region of interest, such as macrophage infiltration in the perivascular adipose tissue (18) and FDG accumulation in adventitial macrophages and brown adipose tissue (19,20). Nevertheless, vascular imaging has the potential to provide a comprehensive assessment of atherosclerosis, including detection of plaque burden, plaque vulnerability, and disease activity. The search for better markers of cardiovascular risk must continue. With the traditional risk factor–based approach in primary prevention, most individuals destined for a near-term heart attack or stroke are misclassified and not identified as being at high risk (21). Consequently, they are not offered appropriate preventive therapy. Detection of subclinical but high-risk atherosclerosis by noninvasive imaging may change this unfortunate situation (22).

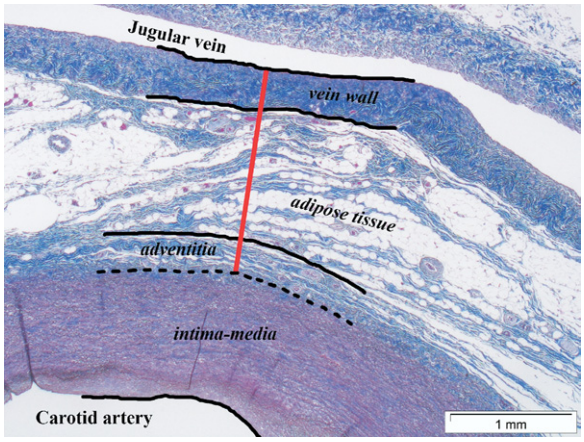

Figure 3. Micrograph of the Area Within the Square in Figure 2

The carotid extra-media thickness (EMT), indicated by the red line, is composed of the vein wall, perivascular adipose tissue, and the arterial adventitia. In this case, adipose tissue constitutes the major component of the EMT, whereas the arterial adventitia constitutes only a minor component. The true dimensions of the individual components cannot be determined by histology because of vascular collaps post-mortem and shrinkage during tissue processing.

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Reprint requests and correspondence: Dr. Erling Falk, Institute of Clinical Medicine, Aarhus University Hospital, Skejby, Brendstrupgaardsvej 100, DK-8200 Aarhus N, Denmark. *E-mail: Erling.Falk@ki.au.dk.*

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Key Words: atherosclerosis ■ carotid artery ■ intima-media thickness ■ adventitita ■ risk assessment ■ obesity.