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EDITORIAL COMMENT

Plaque Composition in the Proximal SFA and Clinical Outcomes in Patients With Claudication

Have We Found the Answer?*

Jihad A. Mustapha, MD, Larry J. Diaz-Sandoval, MD

We can complain because rose bushes have thorns, or rejoice because thorn bushes have roses.
—Alphonse Karr (1)

The prevalence of peripheral artery disease (PAD) is on the rise. According to large-scale trials conducted in the United States and Western countries, the number of patients living with PAD will possibly reach 22 million by 2030 (2–6). The presence of lipid-rich necrotic core (LRNC) and thin fibrous cap has been associated with plaque rupture, thrombosis, and acute coronary events or progression of coronary atherosclerosis (7–10). Because PAD shares many risk factors with coronary artery disease, it is widely assumed to be atherosclerotic in nature, hence its therapeutic approach is based on this assumption. However, it is not known whether the histologic characteristics differ between vascular trees. Arterial calcification is increasingly recognized as a clinically important and complex pathophysiological feature of PAD, as it encompasses 2 distinct disorders: medial (Monckeberg's arteriosclerosis) and intimal (atherosclerotic) calcification, which frequently coexist (11) in varying relative frequencies between vascular beds and conditions such as diabetes and end-stage renal disease (12–14). Arterial calcification (whether medial or intimal is not known) is common in patients with PAD and predicts a worse prognosis.

In this issue of *iJACC*, McDermott et al. (15) report on an elegant multicenter, longitudinal observational study designed to examine 254 patients with evidence of PAD (defined by an ankle-brachial index [ABI] <1.00) to determine the association of magnetic resonance imaging–identified atherosclerotic plaque features in the proximal superficial femoral artery (SFA) with PAD-related outcomes. The investigators should be commended on their attempt to elucidate the pathophysiologic mechanisms through which proximal SFA plaque features could relate to clinical events. Interestingly, the study presents several opportunities to capitalize during future endeavors.

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First, baseline clinical status was loosely defined without the use of widely accepted classifications such as Rutherford-Becker, and for most patients, it did not correlate well with outcomes, questioning the accuracy of the definition: 143 patients (56.3%) had "exertional leg symptoms not consistent with claudication," 70 (27.6%) had claudication, and 41 (16%) were asymptomatic. The amputation rate was 3.14%, comparing poorly with a cohort of patients who underwent femoropopliteal stenting (amputation rate 0.4%) (16).

Second, the investigators conclude that the presence of LRNC in the SFA is associated with PAD-related events whereas calcification is not, although no information is provided regarding its severity and distribution. However, they imaged only the first 30 mm of the vessel using magnetic resonance imaging (which is less sensitive than computed tomography for the detection of calcium) and provide no data regarding the distal vessels, despite knowledge

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From the Metro Health Hospital, Wyoming, Michigan. Dr. Mustapha is a consultant for Cardiovascular Systems, Bard Peripheral Vascular, Cook Medical, Medtronic, Abbott Vascular, Terumo Medical, Boston Scientific, and Spectranetics. Dr. Diaz-Sandoval is a consultant for Cardiovascular Systems and Bard Peripheral Vascular.

that the severity of arterial calcification increases as we progress distally in the arterial tree (17), where computed tomographic detection of calcium correlates with increased risk for amputation (18). Maintenance of long-term patency after femoropopliteal revascularization remains the Achilles heel of endovascular therapy. Nitinol stents have improved results, but lesion morphology remains the most important predictor of long-term outcomes. Long calcified occlusions are associated with the highest incidence of stent fractures (19), especially at Hunter's canal and the P2 segment. Moreover, the constant exposure to simultaneous and opposing biodynamic forces (compression, torsion, flexion, extension, rotation) in the femoropopliteal segment (16) exerts significant stress on metallic endoprostheses, leading to compression, kinking, and fractures with an enhanced inflammatory response that results in accelerated restenosis (20).

Third, the investigators report that the presence of LRNC in the SFA is associated with PAD events independently of PAD severity, which was based on the ABI. Although prior studies show that lower ABI values indicate more severe PAD (21), it has become increasingly clear that among patients with the more severe forms of PAD, ABI is specific but not sensitive, and therefore many patients with severe infrapopliteal disease have "normal ABIs" (22), rendering the assumption by the investigators as a point to learn from.

Last but not least, recent histopathologic studies of patients with end-stage renal disease undergoing lower extremity amputations have found a high prevalence of medial arterial calcification with a very low frequency of intimal atherosclerosis, suggesting that the pathology of PAD differs significantly from the coronary arteries (11). These findings suggest that ischemia can develop in the absence of atherosclerosis and presumably does not arise from plaque rupture. Occlusions were usually due to severe, concentric intimal thickening and/or thrombus. The extensive medial calcification could contribute to occlusions by impairing pulsatile propulsion of blood (leading to blood stagnation, in situ thrombosis, and occlusion) or by preventing outward remodeling of the arteries to accommodate the intimal thickening. These arguments are meant to reflect that it is unlikely that either physiopathologic mechanism is solely responsible for the clinical events of this complex disease, which affects a long segment of arterial tree that is exposed throughout its course to varying physical and mechanical forces, and that perhaps we should change our perspective (we can complain that rose bushes have thorns or rejoice because thorn bushes have roses). Studies with complementary imaging modalities (to allow adequate visualization of both LRNC and calcium) along the entire arterial tree should be conducted to further elucidate the pathophysiology of PAD in order to design segment-specific therapies.

ADDRESS FOR CORRESPONDENCE: Dr. Jihad A. Mustapha, Metro Health Hospital, 5900 Byron Center Avenue, SW, Wyoming, Michigan 49519. E-mail: jihad.mustapha@metrogr.org.

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