Challenges and Opportunities in the Treatment of Vascular Calcification in Peripheral Artery Disease

Disease pathology and epidemiology, diagnosis and classification, treatment options, and novel treatments.

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Vascular calcification (VC) in peripheral artery disease (PAD) presents a treatment challenge. This is especially true because VC is ubiquitous, found in up to 47% to 72% of PAD patients.[1-3] The pathophysiology of VC was previously attributed to elevated serum calcium levels; however, this theory has recently fallen out of favor. Calcification of the vasculature is triggered by inflammation as an active pathologic response to systemic disease. When it occurs, calcium deposition is typically seen in two of the three anatomic layers of arteries, specifically the intima and media. Intimal calcification occurs in association with a classically obstructive atherosclerotic plaque. Medial calcification (Mönckeberg sclerosis) is more prevalent in intra-abdominal and lower extremity arteries, and the complex pathophysiology of medial arteriosclerosis is thought to be associated with an upregulation of bone-associated proteins and osteoblast differentiation factors.[2,4] More specifically, associated mechanisms of medial VC include an accompanying decrease in inhibition of antimineralization factors, such as pyrophosphate, which is expressed by blood vessels. Secondly, activation of vascular osteoblast-like cells induces mineralization of vascular smooth muscle cells.[5] Increased bone turnover leads to the release of circulating nucleational complexes that act with apoptotic cells as substrate for VC.[5]

The distribution of medial calcification extends contiguously throughout the vascular bed, resulting in arterial stiffening and decreased compliance. Medial VC is more commonly seen in the femoral artery than the popliteal artery and poses special challenges when it is present below the knee (which is common) since it affects both diagnostic accuracy (eg, noncompressible vessels lead to falsely elevated ankle-brachial index [ABI]) and interventional considerations. Its prevalence increases with age and in patients with diabetes mellitus, chronic kidney disease, obesity, and dyslipidemia.[2,3]

It is well known that the presence of PAD correlates with cardiovascular mortality, and this holds true even when correcting for coexisting cardiovascular risk factors and can help prognosticate potential outcomes.[6] Alternatively, a meta-analysis by Renneberg et al demonstrated that arterial or valvular calcification carries a separate additional risk of broad cardiovascular events and mortality, and Yang et al showed that just the presence of VC was linked to not only mortality but also limb-specific outcomes, with increased risk of limb amputation in patients with PAD.[7,8]

DIAGNOSIS AND CLASSIFICATION OF VC

The ABI is a simple test to begin the diagnostic workup of PAD and VC. Although an ABI < 0.9 is indicative of PAD, VC can contribute to an increase in ABI > 1.3 due to noncompressible lower extremity arteries.[9] The exact anatomic location and severity of a lesion can then be visualized with noninvasive imaging modalities. Extravascular ultrasound (EVUS) can noninvasively

identify the extent and location of calcific lesions, but the shadowing of the lumen by calcium may limit the ability to determine systolic flow velocities in the underlying vessel.[10] CTA identifies calcium very well when used as an adjunctive noninvasive diagnostic test; however; extensive VC decreases the diagnostic accuracy of CTA because it creates a "blooming artifact," which can make the lesion appear more severe. This can be largely addressed by modified acquisition protocols and image postprocessing (ie, window adjustments).[11]

Diagnostic angiography is the standard invasive diagnostic tool but can underestimate the calcium burden because most angiography is taken in only an anteroposterior imaging plane and will miss orthogonal calcium.[12] In addition, assessing fluoroscopic calcium density is typically done by visual estimation and not objectively quantified, therefore introducing marked interobserver variation. To overcome this problem, intravascular ultrasound (IVUS) is being increasingly utilized to measure the extent of VC intravascularly but has yet to be correlated with angiography to validate existing classifications.[13]

Several angiographic classifications have been developed to objectively quantify the degree and distribution of calcium. The most commonly used scoring systems are the Peripheral Arterial Calcium Scoring System and the Peripheral Academic Research Consortium.[2,14] Other scoring systems have been developed to quantify clinical outcomes in trials; however, there remains no uniformly accepted classification. The lack of consistency in scoring systems may be attributable to the limited anatomic and outcome evidence validating any of the proposed scales. Therefore, comparing the results of studies is difficult given the heterogeneity in documentation of calcification burden.[15] Furthermore, the clinical implications of the various grades of calcification have not been definitively elucidated.

TREATMENT OPTIONS

Current treatment paradigms of PAD target the luminal narrowing of the affected artery. Aggressive lifestyle changes, treatment of underlying comorbidities such as chronic kidney disease, diabetes mellitus, and hypertension, along with supervised exercise are the backbone of noninvasive PAD treatment. In addition, antiplatelet and/or anticoagulant and statin therapy are indicated in all PAD patients. The available medications to reduce claudication symptoms are sparse, but the vasodilator cilostazol is effective in decreasing claudication symptoms and increasing walking distance. Notably, it has been recently shown that there is a role for low-dose rivaroxaban in PAD patients after revascularization. Rivaroxaban improved cardiovascular and limb-specific outcomes including acute limb ischemia and amputation in the recent VOYAGER PAD trial, and this has led to its approval by the FDA for this indication.[16]

Endovascular revascularization is reserved for patients with lifestyle-limiting claudication not adequately relieved with conservative therapy and critical limb ischemia.[17] Endovascular revascularization modalities include percutaneous transluminal angioplasty, drug-coated balloon (DCB) angioplasty, drug-eluting or bare-metal stenting, and atherectomy. As successful as these interventions can be in achieving revascularization and relieving clinical ischemia, VC is associated with more procedural complications and long-term treatment failure. The calcification in chronic arterial occlusions makes navigating guidewires across the stenosis difficult and more often causes the wire to be diverted from its intraluminal course. The decreased compliance of calcified vessels requires higher pressures for balloon expansion during angioplasty, which increases the risk of arterial wall dissection and perforation because the nonaffected wall will give way first to the high-pressure balloon. Dissection is managed by placing a stent, which has the potential to fracture due to its interaction with the VC and further complicate future revascularizations. The stent may also not achieve full expansion, increasing the potential for restenosis and making reintervention difficult. Importantly, Fanelli et al demonstrated that VC appeared to decrease the efficacy of DCBs due to the reduced absorption of antiproliferative agents.[18]

As an alternative, atherectomy can be utilized in lesions with VC, and there are multiple methods available. For example, excisional atherectomy cuts plaques directionally and may be preferred in eccentric rather than circumferential lesions. The excised plaque is collected in the nose cone of the device and retrieved. Due to the lack of catheter aspiration, this technique carries a significant risk of distal debris embolization. Therefore, distal filter devices are frequently used to prevent embolization.[19] Another approach utilizes rotational aspiration/atherectomy catheters, which feature a rapid front-cutting drill that allows for passage through high-grade stenoses as well as thrombotic lesions. Examples of such catheters include the Jetstream atherectomy system (Boston Scientific Corporation) or Rotarex S (BD Interventional). Both systems remove debris through continuous suction, which decreases embolization and can limit the necessity of distal filter placement. Another mechanism is laser atherectomy, which has two mechanisms of action: (1) high-energy

light that directly ablates plaques and calcification and (2) light energy that is absorbed by blood or contrast and exerts a mechanical effect.[20] Rotational and orbital atherectomy utilize spinning or oscillating diamond-coated crowns, respectively, to ablate the calcific plaque to allow for lower-pressure balloon (and more effective) angioplasty.[21-24]

Although atherectomy appears to reduce stent implantation compared to vessel preparation with PTA, it has not been extensively studied in calcified lesions and thus randomized data are lacking with regard to clinical outcomes.[25,26] This dearth of data in high VC lesions is actually present for most interventional tools. Trials tend to exclude these patients because calcification is a confounder that can independently increase undesirable complications frequently seen in the endovascular treatment of PAD with a high calcium burden. This limits the development of an evidence-based treatment approach for this underrepresented patient population.

NOVEL APPROACHES IN VC TREATMENT

A novel treatment strategy of calcific lesions includes catheter-guided intravascular lithotripsy (IVL) followed by balloon angioplasty. Lithotripsy is a medical procedure commonly used in urologic interventions to fragment kidney stones with shockwaves. The intra-arterial utilization of this technique aims to crack/modify calcified plaques by delivering very short bursts of very high pressure (50 atm) to the vessel wall through a low-pressure, fluid-filled balloon inflation. This action allows for facilitated balloon expansion and a decreased risk of arterial dissection and perforation.[27] The resulting in situ fragmentation of the calcium is also hypothesized to improve the delivery of antiproliferative medications by DCB.[19]

After two exploratory trials, the pivotal DISRUPT PAD III trial randomized patients between IVL with DCB versus standard PTA with DCB in patients with moderate to severely calcified PAD. The primary outcome was procedural success defined as < 30% residual stenosis without flow-limiting dissection. The primary endpoint was met in 68% of patients in the IVL group and in 52% of the PTA group. Concomitantly, there was a relative risk reduction of 77% for type C and D dissections, which resulted in a reduction in stent placement.[28] One-year results evaluating the patency of treated stenosis are pending and will reveal the long-term success of IVL as an adjunct to DCB effectiveness.

CONCLUSION

VC is commonly seen in PAD. It is associated with numerous challenges in diagnosis, quantification of disease, classification ambiguity, and choice of effective treatment strategies. There is a lack of data regarding a validated treatment approach despite common intervention failures and decreased long-term vessel patency. Finding an effective treatment approach for peripheral arterial calcification poses an important challenge in an aging population with increased prevalence of the two most significant risk factors: chronic kidney disease and diabetes mellitus. Recently, IVL has been shown in the only randomized data available in this population to offer an advantage over the standard treatment strategies by delivering a better PTA result while overcoming common complications. Long-term data will determine its efficacy as an enhancement to preventing restenosis. Further studies are needed to validate current diagnostic and treatment modalities combined with further development of innovative therapies to combat VC in PAD. ■

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