

Calcium: Why It Matters

By Fabrizio Fanelli, MD, EBIR

Vascular calcification, traditionally known as *ossification of the arteries*, is a progressive accumulation of calcium and phosphate within the arteries that is associated with mineral deposits both in the intima and media layers of the vessel wall. Its physiological development and clinical treatment remain active areas of research. Chronic kidney disease and diabetes mellitus are the main causes of vascular calcification; however, vascular calcification is a pathologic process that occurs in response to dysregulated or inappropriate environmental stimuli and an atherogenic risk profile that includes advancing age, atherosclerosis, dyslipidemia, and genetic diseases. Besides the vasculature, where calcium contributes to atherosclerotic disease, calcium can accumulate in other organs such as the spleen, liver, and kidney.

ETIOLOGY AND PATHOPHYSIOLOGY

Vascular calcification is the pathologic response to toxic stimuli involving metabolic substances and/or inflammatory cells. Similar to the process of bone formation, vascular calcification consists of a complex, intracellular molecular process that includes the differentiation of macrophages and vascular smooth muscle cells into osteoclast-like cells. Vascular

calcifications are divided into intimal and medial (Mönckeberg medial sclerosis) morphologies. Intimal calcification is associated with atherosclerotic plaques and is thought to result from modified lipid accumulation, proinflammatory cytokines, and apoptosis within the plaque that induces osteogenic cell differentiation. The most recognized function of intimal calcification is isolation and interruption of the abnormal cellular process, thus protecting healthy adjacent intima. Medial calcification is considered to be more widespread in the lower abdominal region. Associated with peripheral artery disease, medial calcification results from the osteogenic differentiation of smooth muscle cells within the medial layer of the vessel wall. Although medial calcification is generally not linked to luminal obstruction, the decrease in wall elasticity and compliance of the arterial vessel can ultimately lead to atherosclerosis and reduced perfusion.

WHY CALCIUM MATTERS

Calcium is a well-known enemy of endovascular procedures. Underdiagnosed and underestimated by angiography, calcium makes a vessel resistant to dilatation and susceptible to recoil and embolism. Importantly, calcium is significantly responsible for the occurrence of dissections. In fact, 71% of flow-limiting dissections occur within a calcified vessel because the presence of calcium dramatically reduces the arterial wall elasticity and the vessel cannot be compliant when a balloon is inflated. This problem has gained renewed attention with the introduction of drug-coated balloons (DCBs), especially when optimal balloon angioplasty is required to reduce the number of stents implanted. Moreover, calcified lesions present numerous challenges, including responding poorly to balloon angioplasty, requiring frequent use of stents, exhibiting a high incidence of angiographic complications, and limiting the effectiveness of DCBs.

Several technical advantages of DCBs have been described in their mode of action, such as the ability to achieve a uniform distribution and release of drug on

the arterial surface, and ultimately their ability to achieve arterial patency with provisional use of stents. However, even in the era of drug elution, calcium is still a potential barrier to optimal drug absorption after the use of DCBs. In particular, circumferential distribution of calcium, as opposed to longitudinal extension of calcium, appears to be a strong predictor of patency loss. These results have rendered primary stenting the preferred strategy in these settings. Nonetheless, once the stent is deployed, calcium continues to cause further challenges, with risks of malapposition, suboptimal expansion, and an increased likelihood of stent fractures.

ADDRESSING CALCIUM

To increase the efficacy of the endovascular approach in the presence of calcification, vessel preparation with atherectomy or a debulking system is very promising. These techniques can improve vascular remodeling, enhance drug diffusion in the vessel wall, and promote the antiproliferative drug effect. Physiologically, the results are reduced stenosis and improved tissue perfusion, while the clinical benefits include increased walking distance in claudicants, accelerated wound healing, and improved limb salvage in patients with critical limb ischemia.

CONCLUSION

In summary, vascular calcification associated with atherosclerotic disease is a progressive pathologic process that affects arterial wall compliance and elasticity and subsequently impairs tissue perfusion. Well-known risk factors, such as chronic kidney disease and diabetes mellitus, exacerbate the condition of vascular calcification, and clinically, this condition is associated with decreased walking distance, impaired wound healing, and reduced limb salvage. As a barrier to both traditional mechanical endovascular approaches, such as balloon angioplasty,

as well as drug-eluting therapies, like DCBs, vascular calcification deserves special attention from vascular specialists charged with treating patients exhibiting this difficult lesion morphology.

Recommended Reading

- Cioppa A, Stabile E, Popusoi G, et al. Combined treatment of heavy calcified femoropopliteal lesions using directional atherectomy and a paclitaxel coated balloon: one-year single centre clinical results. *Cardiovasc Revasc Med*. 2012;13:219-223.
- Fanelli F, Cannavale A, Gazzetti M, et al. Calcium burden assessment and impact on drug-eluting balloons in peripheral arterial disease. *Cardiovasc Intervent Radiol*. 2014;37:898-907.
- Fitzgerald PJ, Ports TA, Yock PG. Contribution of localized calcium deposits to dissection after angioplasty. An observational study using intravascular ultrasound. *Circulation*. 1992;86:64-70.
- Fonseca A, Costa Jde R, Jr, Abizaid A, et al. Intravascular ultrasound assessment of the novel AngioSculpt scoring balloon catheter for the treatment of complex coronary lesions. *J Invasive Cardiol*. 2008;20:21-27.
- Kashyap VS, Pavkov ML, Bishop PD, et al. Angiography underestimates peripheral atherosclerosis: lumenography revisited. *J Endovasc Ther*. 2008;15:117-125.
- Raman R, Raman B, Napel S, Rubin GD. Semiautomated quantification of the mass and distribution of vascular calcification with multidetector CT: method and evaluation. *Radiology*. 2008;247:241-250.
- Roberts D, Niazi K, Miller W, et al. Effective endovascular treatment of calcified femoropopliteal disease with directional atherectomy and distal embolic protection: final results of the DEFINITIVE Ca⁺⁺ trial. *Catheter Cardiovasc Interv*. 2014;84:236-244.
- Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. *Catheter Cardiovasc Interv*. 2014;83:E212-E220.
- Tepe G, Beschoner U, Ruether C, et al. Drug-eluting balloon therapy for femoropopliteal occlusive disease: predictors of outcome with a special emphasis on calcium. *J Endovasc Ther*. 2015;22:727-733.
- Tepe G, Zeller T, Schnorr B, et al. High-grade, non-flow-limiting dissections do not negatively impact long-term outcome after paclitaxel-coated balloon angioplasty: an additional analysis from the THUNDER study. *J Endovasc Ther*. 2013;20:792-800.

Fabrizio Fanelli, MD, EBIR

**Vascular and Interventional Radiology Unit
Department of Radiological Sciences
"Sapienza" University of Rome**

Disclosures: Consultant, speaker, and advisory board member for Medtronic, Cook Medical, Bard Peripheral Vascular, Boston Scientific Corporation, Shockwave Medical, and Spectranetics Corporation.