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EDITORIAL COMMENT

Shaking and Breaking Calcified Plaque

Lithoplasty, a Breakthrough in Interventional Armamentarium?*

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Calcium has always been the worst enemy of the interventionist; calcium impedes crossability, expansion, embedment, and coverage (1,2).

Fluoroscopy severely underestimates the presence of endoluminal calcium, and the calcium detected on fluoroscopy is sometimes localized at the interface between the adventitia and the media (i.e., Mönckeberg arteriosclerosis) (3). Intravascular ultrasound is the most reliable diagnostic tool to detect endoluminal and deep calcium, but the leading edge of the endoluminal calcium hides in its shadow the actual mass of calcium in the vessel wall (4). Optical coherence tomography (OCT) has a limited depth penetration but can, with a high sensitivity and specificity, image superficial calcium and assess the back side of the calcified plaque, rendering possible the measurement of the total calcified mass (4). These last 2 techniques are intravascular and are still used in a minority of patients. In the near future, multislice computed tomography (MSCT) could be used to define the calcium load along the luminal pathway and indicate to the interventional cardiologist the plan to follow in treating these calcified plaques (rotational atherectomy, orbital atherectomy, lithoplasty) (**Figure 1**).

Although rotational atherectomy (RA) was expected to be one of the solutions, the landmark trial ROTAXUS (Rotational Atherectomy Prior to TAXUS Stent Treatment for Complex Native Coronary Artery Disease) did not demonstrate any improvement in clinical outcomes (5). At 2 years, major adverse cardiovascular events (MACE) and target-lesion revascularization occurred in 29.4% versus 34.3% ($p = 0.47$) and 13.8% versus 16.7% ($p = 0.58$) in the RA group and the standard therapy group, respectively. Afterward, orbital atherectomy (OA) was introduced. In the single-arm ORBIT II (Evaluate the Safety and Efficacy of OAS in Treating Severely Calcified Coronary Lesions) trial, 2-year rates of MACE and target-lesion revascularization were 19.4% and 6.2%, respectively (6). Comparison of the data of first-generation drug-eluting stents in ORBIT II (17.2%, $n = 74$) with ROTAXUS (29.4%, $n = 120$) indicated numerically lower event rates in ORBIT II. Several potential advantages of OA over RA were the adjustable ablation diameter, continuous blood flow during ablation, smaller particle size, and lower incidence of slow flow/no-reflow. However, OCT analysis has demonstrated eccentric lesion modification by RA (7,8) and OA (9,10) that follows the guidewire course (guidewire bias) (**Figure 2**). In regions of tortuosity or eccentric plaque, crater, or tunnel formation could occur after RA or OA, which could lead to perforation or stent malapposition.

Recently, as a new approach of vessel preparation before stent implantation in calcified lesion, lithotripsy-enhanced disruption of calcium (i.e., lithoplasty) was introduced. The lithoplasty catheter is a balloon angioplasty catheter with unfocused lithotripsy emitters, which disrupts both superficial and deep calcium within vascular plaque by acoustic circumferential pressure pulses. Lithotripsy does not rely on mechanical tissue injury by physical interaction, such as RA, OA, cutting balloon, or scoring balloon, but rather by a diffuse acoustic pulse through a balloon inflated to 4 to 6 atm. There are currently 2 studies evaluating the safety and performance of the lithoplasty catheter: DISRUPT PAD (Safety and Performance Study of the Shockwave Lithoplasty System) and DISRUPT CAD (Shockwave Coronary Rx Lithoplasty Study). DISRUPT PAD is

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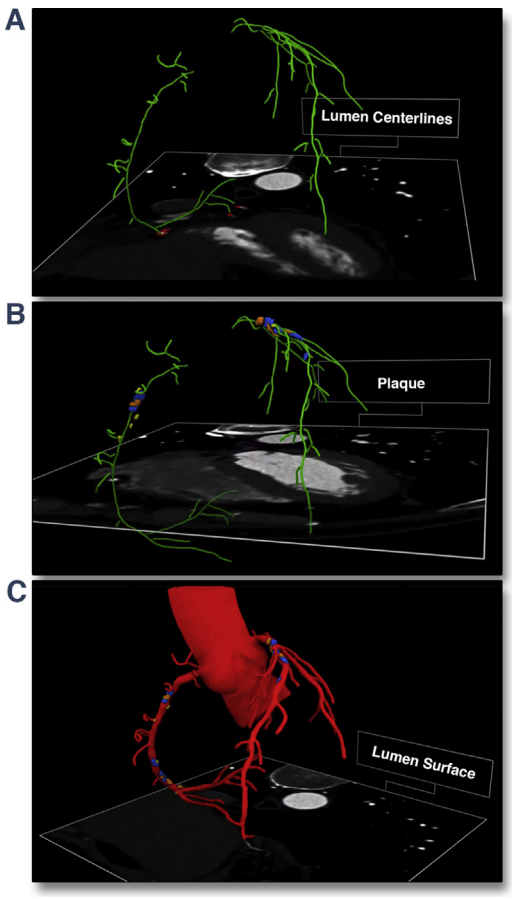
FIGURE 1 A Concept of Coronary Calcium Mapping in Multislice Computed Tomography



(A) Luminal centerline. **(B)** Mapping of plaque and calcium location (as a function of Hounsfield units). **(C)** Rendering of luminal surface in relation to plaque location.

a multicenter, prospective, single-arm study applying the lithoplasty catheter to the treatment of calcified femoropopliteal lesions. Procedural success was achieved in 100.0% of cases, and 96.8% were free from target-lesion revascularization at 6 months. DISRUPT CAD is a multicenter, prospective, single-arm study of percutaneous lithoplasty before stent implantation in heavily calcified coronary lesions. The primary safety endpoint is rate of MACE within 30 days of the procedure, and the primary performance endpoint is clinical success, defined as residual stenosis <50% after stenting with no evidence of in-hospital MACE. The main result has not been published but was presented at TCT 2016 as a 5% 30-day MACE rate and 95.0% clinical success.

In this issue of *iJACC*, Ali et al. (11) present the OCT substudy from the DISRUPT-CAD trial. After lithoplasty, intraplaque calcium fracture was observed, and its frequency increased as the calcification severity increased. Final stent expansion was similar among all tertiles of calcification severity, which suggests more efficacy with increasing severity of calcification. This report is important because it is the first experience with a lithoplasty device to address the unmet need in treatment of severely calcified lesions.

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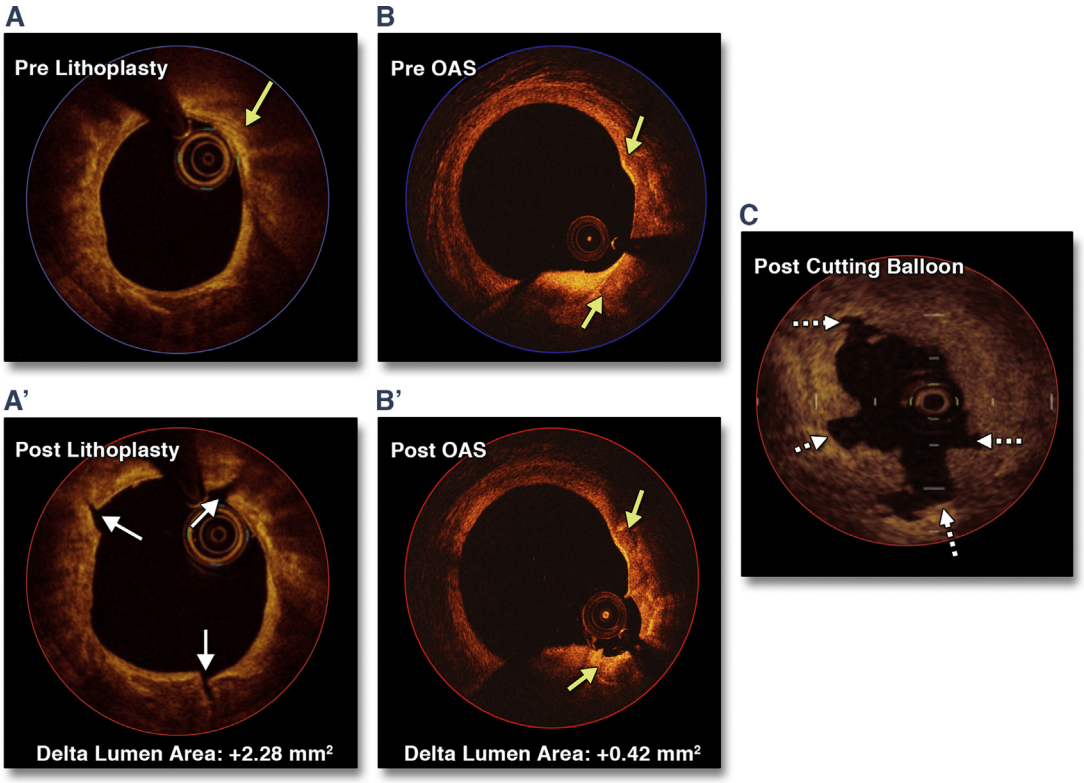
With the introduction of scaffold technology, preparation of the lesion and sizing of the device are now of paramount importance, and highly calcified lesions are not themselves a contraindication for treatment provided the preparation creates a circular and concentric lumen (**Figure 3**). The concept of circumferential plaque modification is welcome, especially in the era of bioresorbable scaffolds. Although bioresorbable scaffolds appeared to overcome the limitations of permanent metallic stents, their use technically requires more extensive lesion preparation in calcified lesions because of their limited mechanical strength and radial force (12). Suwannasom et al. (13) demonstrated post-procedural lesion asymmetry was an independent predictor of the device-oriented composite endpoint. Lesion asymmetry remained even after 5 years post-procedure, which suggests the impact of lesion preparation before device implantation (14). Therefore, there is a resurgence of the use of atherectomy for the purpose of optimal lesion preparation among patients undergoing implantation of bioresorbable scaffolds. These publications raised again the question of whether OCT guidance should become universal (more and more commonly used for sizing and guidance during the preparation phase preceding the implantation of a stent or scaffold).

Coronary angiography, the Mason Sones' discovery that has revolutionized the diagnosis and treatment of coronary artery disease, is now more than one-half century old and should be used in conjunction with OCT; it can be preceded by MSCT, which can be used the day before catheterization to indicate the angiographic view that would be optimal for treatment of the lesion. In the United Kingdom, the National Institute for Health and Care Excellence has promoted MSCT with fractional flow reserve derived from computed tomography as the most cost-effective diagnostic approach for coronary artery disease.

FIGURE 2 Optical Coherence Tomography Comparison of Lithoplasty, Orbital Atherectomy, and Cutting Balloon



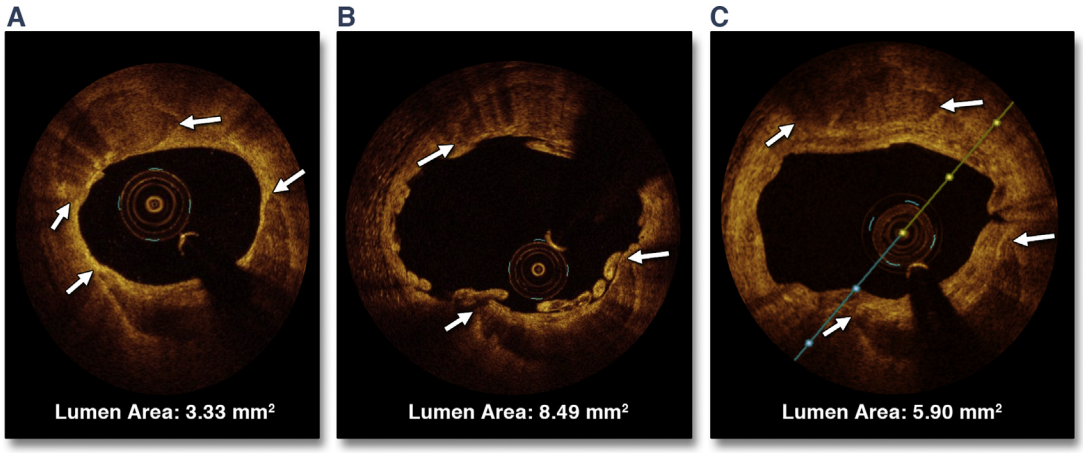
(A) Pre-lithoplasty; **yellow arrow** indicates calcium. **(A′)** Post-lithoplasty; **white arrows** indicate crackles made by lithoplasty balloon (11). **(B)** Pre-orbital atherectomy; **yellow arrow** indicates the edge of calcium. **(B′)** Post-orbital atherectomy (10). Note that the lumen expands circumferentially in lithoplasty, whereas orbital atherectomy system (OAS) ablated the vessel wall only near the guidewire. **(C)** Post-cutting balloon inflation. Multiple tears **(white dashed arrows)** in the intima were observed after dilatation with a cutting balloon (reprinted with permission from Terashima et al. [15]).

This new technique of decalcification opens new avenues of diagnosis and treatment. However, every new technique can potentially be confronted with a new "enemy," and the publication by Ali et al. (11) raises numerous questions that we now address.

In this mechanistic and imaging study, no investigation of possible embolization was conducted (coronary flow reserve pre- and post-lithoplasty and collection of high-sensitivity troponin). This information might become available in the main (unpublished) paper.

It is evident that in the future, comparisons (randomized or not) will be made to assess the respective decalcification/ablation capability of lithoplasty, rotablation with a circular or elliptical burr, and cutting balloons, of which the impact on calcium must also be documented by OCT (**Figure 2C**) (15). In that respect, the dynamic compliance of delta-inflation pressure versus delta-balloon diameter of the pre-treated lesion during device (stent/scaffold) implantation should be analyzed by cine filming the balloon inflation while recording the pressure. The assessment of the fracture generated by lithotripsy and the cut caused by the cutting balloon will need to be differentiated and assessed quantitatively in a reproducible fashion, as dissection characteristics have been categorized (depth, length, width) and quantified in the literature (16). At the present stage of investigation, it seems the gain in lumen area is substantial (2 mm^2) and circumferential, judging from the OCT image. It is assumed that the profile and crossability of the device are satisfactory, although the profile of the device and the device success are not reported in the present publication. As opposed to the

FIGURE 3 Optical Coherence Tomography Image of a Calcified Lesion Treated With a Bioresorbable Scaffold* (17)



(A) Pre-procedure. There was a 90° calcium arc between 9 and 12 o'clock and a 180° calcium arc between 3 and 8 o'clock. **(B)** Post-procedure. The balloon and scaffold treatment was able to separate the 2 areas of calcium by stretching the free wall between severe calcifications. **(C)** At follow-up, the separation and stretching effect is maintained; **white arrows** indicate the edges of the calcified plaque. *Mirage BRS (Manli Cardiology, Singapore).

rotablator, no specific guidewire is needed for the lithoplasty, and from that point of view, the technique appears to be more user friendly.

All of these questions will have to be investigated and resolved. It is today favorable and beneficial for the interventional cardiologist and their patients that various techniques of decalcification/ablation become commercially available and compete with each other. However, there is still a long way to go from first-in-human studies (safety, feasibility, and potential efficacy) to surrogate assessments (e.g., circular, concentric lumen areas) in randomized comparisons with a plain noncompliant balloon with high pressure (not to mention scoring, cutting balloon, orbital atherectomy, or rotablation), to the demonstration of an incremental benefit in clinical outcome in a randomized comparison with … etc.

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