New Advances in the Treatment of Severe Coronary Artery Calcifications

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KEYWORDS

- Coronary artery calcification calcific lesion • IVUS • OCT • Coronary atherectomy
- Intravascular lithotripsy

KEY POINTS

- Coronary artery calcifications challenging scenarios.
- Intracoronary imaging is necessary to understand calcific lesion features.
- Accurate evaluation of lesion characteristics is crucial.
- Evaluate calcific arc, length and thickness before percutaneous coronary intervention.
- Plaque modification can be achieved with different devices before stent and optimization.

INTRODUCTION

Coronary artery calcification (CAC) is associated with adverse cardiovascular events. It is part of 2 distinct processes: calcific atherosclerosis and medial artery calcification, etymologically the word atherosclerosis derives from the Greek word for gruel (ἀθήρα, atèra) and hardening (σκλήρωσις, sklèrosis).

Calcific atherosclerosis occurs in the intima and is inflammatory-dependent. Medial artery calcification is related primarily to age, male sex, Caucasian ethnicity, diabetes mellitus and chronic kidney disease (CKD).

Vascular calcification is remarkably accelerated and contributes to a higher risk of cardiovascular morbidity and mortality.[1,2]

Coronary calcification is localized within intimal plaque except in patients with CKD who develop principally medial and intimal calcific layer.[3]

Constant healings and modifications of plaques after ruptures or hemorrhages lead to development of obstructive fibro-calcific lesions, common in patients with chronic angina and sudden cardiac death.[4,5]

Understanding plaque characteristics and distribution is crucial to select a “plaque modification strategy” before stent implantation to minimize malapposition.[6]

CALCIFIC LESIONS PHONOTYPES

Calcium regulatory mechanisms that affect bone formation influence coronary artery calcification, made by hydroxyapatite, carbonate apatite, and calcium-deficient apatite. “Eccentric calcium” occurs involving less than 270° of lumen perimeter. “Concentric calcium” is a cross-section involvement of lumen with greater than 270° of calcium.

High-pressure ballooning can achieve calcium fracture in the thinner areas. Atherectomy based

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procedures aim to partially ablate the calcium allowing the fracture of calcified structures and permitting further luminal gain.

IMAGING OF CORONARY CALCIFIC LESION

Accurate evaluation of coronary lesions is crucial to perform perfectly planned percutaneous coronary intervention (PCI). Particularly rich mineral content CAC are detected by fluoroscopic methods; calcium creates radio-opacities noted before contrast injection. Intravascular ultrasound (IVUS) is more accurate than angiography for detection of calcific lesions, with sensitivity of 90% to 100% and specificity of 99% to 100%.[3,7] Clinical data demonstrate the enhanced sensitivity of IVUS in detecting coronary calcium compared with angiography (73% of cases vs 38%; *P*<.001).[4]

Calcium reflects ultrasound, recognized as a bright echo with acoustic shadowing.[5] Moreover IVUS provides discrimination of deep versus superficial calcium, thickness cannot be evaluated using IVUS. The calcium arc is classified as follows: none or involving 1 quadrant (0° to 90°), 2 quadrants (91° to 180°), 3 quadrants (181° to 270°), or 4 quadrants (271° to 360°). Calcium location is superficial if present in the intimal-luminal interface, or deep if within the medial-adventitial border or closer to the adventitia than the lumen, or even both superficial and deep.[6] Calcium thickness cannot be determined directly with IVUS and volume cannot be calculated with the same accuracy of optical coherence tomography (OCT).

For this reason, historically calcific arc circumference detected by IVUS was considered a very important parameter, an arc greater than 180° could predict a probable risk of stent underexpansion.[8]

In the PROSPECT study (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) patients with higher dense calcium volumes were more likely to have higher rates of major adverse cardiovascular events (MACE) at 3 years.[9–11]

OCT offers high spatial resolution imaging (10–20 mm), better than IVUS (150–200 mm). Intravascular frequency domain OCT is the finest modality for the assessment of coronary calcium distribution.

Definition of calcific arc degree detected with IVUS is well integrated with OCT parameters such as calcium thickness, calcium length, and calcium 3-dimensional volume that correlate negatively with stent expansion and correct response to balloon dilation. Particularly, Fujino and colleagues[12] combined calcific arch greater than 180° (2 points), calcific thickness greater than 0.5 mm (1 point), and calcific longitudinal length greater than 5 mm (1 point) to create a scoring system that can predict higher risk of stent underexpansion, more observed in calcific lesions reaching score of 4. The interaction between calcium arc and thickness is important to predict the success of cracking the calcific layer with a conventional balloon. As shown by Maejima and colleagues[13] calcium cracks after balloon angioplasty were associated with a greater arc and a thinner minimal thickness of the calcium component.

NEW TREATMENT ERA OF CORONARY CALCIFIC LESIONS

Calcification makes difficult to deliver devices and increases the risk of PCI failure.

One in 4 patients undergoing PCI presents a calcific lesion. Heavily calcified lesions are a particular threat for drug-eluting stents, damaging the polymer/drug coating during tough advancement and subsequently allowing only poor diffusion of the drug to the subintima.[14–16]

Calcified lesions are associated with increased intraprocedural complications such as underexpansion, asymmetrical expansion, malapposition and postprocedural risk of in-stent restenosis and thrombosis.[17–20] Asymmetrical calcific lesions predispose to coronary dissection or perforation.[21,22]

Calcified lesions can be approached with success and procedural good accomplishment.[23]

WIRE SELECTION

Frequently “workhorse” guidewires are adequate for most CAC, but in cases with significant angulation or tortuosity, hydrophilic coating guidewires may facilitate manipulation. If this option is not successful, “buddy” guidewire or deep coronary intubation with a child-in-mother catheter could be an easy solution.

In case of severe CAC also microcatheters for lesion crossing so that the operator can exchange finer wires required for atheroablative devices.

If microcatheter does not cross, an 0.009-inch RotaWire (for rotational atherectomy; Boston Scientific, Natick, MA) or 0.012-inch ViperWire (for orbital atherectomy; Cardiovascular Systems, Inc., St. Paul, MN) and directly proceed to atheroablation.

BALLOON ANGIOPLASTY FOR CORONARY ARTERY CALCIFICATIONS: NOT JUST UNDER PRESSURE

With common balloon for angioplasty, the forces privilege less hard parts, preferentially not involved by CAC. Resistances to radial forces may bring to several complications. Noncompliant balloon (NCB) can tolerate high inflating pressures without increasing too much in diameter, uniformly expanding the coronary segment.

OPN NC balloon (SIS Medical, Frauenfeld, Switzerland) is a rapid exchange percutaneous transluminal coronary angioplasty device, with its unique twin-layer technology can allow super high pressure (to 4560 kPa) with very poor diameter expansion, dedicated especially for in-stent restenosis (ISR), it has nominal pressure at 10 atm and a rated burst pressure of 35 atm. It available in various diameters ranging from 1.5 to 4.5 mm and 3 lengths: 10, 15, 20 mm. The limitation of the OPN balloon is the high profile that undermines any attempt to recross when inflated.[24]

OPN NC high-pressure balloon can be easily used in case of the failure of conventional balloons, providing a safe and easy alternative strategy in case of failure of conventional NC balloon dilatation.[25]

However, CAC may become resistant to further high-pressure dilatation after compression.

In 1990s, medical technology brings to light a new modified noncompliant balloon provided of sharp microblades (∼0.25 mm in height) settled longitudinally on the surface, called Flextome Cutting Balloon, as a newborn called Wolverine balloon, with a cutting functional height of 0.005 foot, available in monorail and over-the-wire, with 3 different blade lengths: 6, 10, 15 mm. When inflated the cutting balloon creates radial incision on the fibrocalcific plaque, allowing expansion with conventional balloon minimizing elastic recoil of vessel. Cutting balloon angioplasty (CBA) is used to treat mainly fibro-calcific plaque or in ISR.[26]

For dilatation of various kind of hard lesions, it was designed the AngioSculpt scoring balloon (AngioScore, Fremont, CA), an innovative device consisting of a double lumen catheter with a semicompliant, nylon balloon surrounded by an external nitinol-based helical scoring edge, thought to be more flexible and manageable. This technology decreased incidence of balloon slippage, a more uniform balloon expansion, reducing elastic recoil and an optimal postinflation minimal lumen diameter.

AngioSculpt is available in 3 different lengths of 10, 15, and 20 mm and balloon diameters from 2.0 to 3.5 mm. Radiopaque markers demarcate the proximal and distal edge of the balloon for fluoroscopic visualization. During balloon deflation, the nitinol cage has an active role in the device deflation.

The indications of scoring balloons are growing with operators experience, but nowadays this technique is meant for lesion preparation before stenting: complex vessels or in select cases of ISR and bifurcation lesions, promising are its adapted uses in valvuloplasty and drug-covered balloon technologies.

ATHERECTOMY TECHNIQUES

Rotational Atherectomy

In the past 3 decades rotational atherectomy (RA) has represented the main atheroablative technique for high calcium content coronary lesions. Few modifications to its essential mechanics have been imported, but significant incremental improvement in technique has been introduced. The current RA system available is the *Rotablator System* (Boston Scientific, Natick, MA). RA has recently evolved as a unique tool for calcified coronary lesions, with a new entity called RotaPro system.

This unique device is composed of a diamond-encrusted elliptical burr on the top that rotates at high speeds. The burr is tracked over a 0.009-inch guidewire, placed across the lesion, it crosses many times the calcified lesions with rotational speeds of 140,000 to 150,000 rpm.

Rotational atherectomy bases its functional principle on the concept that different components (such as for example, fibro-calcific lesion and calcium deposits) have an altered elasticity.[27] The burr prefers to ablate inelastic materials, sparing healthy part.[27,28] Thus, hard and inelastic plaques are rigid and can be pulverized preferentially. Its main and primary use is to facilitate balloon angioplasty and correct stent deployment. The STRATAS study (Study to Determine Rotablator and Transluminal Angioplasty Strategy) compared outcomes of an aggressive versus routine strategy (maximum burr:artery ratio >0.70 alone or with adjunctive balloon inflation $\leq$1 atm vs maximum burr:artery ratio $\leq$0.70 with routine balloon inflation $\geq$4 atm). There were no advantages for clinical success, final minimum lumen diameter, or residual stenosis, and there were higher rates of periprocedural creatine kinase-myocardial band release and target lesion revascularization (TLR) at 6 months.[29]

The CARAT (Coronary Angioplasty and Rotablator Atherectomy Trial) was on the same line, aggressive strategy does not pay back.[30]

RA stepped away from aggressive debulking permitting development of smaller burrs, sheaths, and guide catheters with much more safety and efficiency, moving toward a “modification approach of CAC.”

Rotational modification of calcium and preparation of lesion is meant to enable drug-eluting stent delivery therefore reducing ISR, but in several trials the beneficial effect is not well established.

ROTAXUS trial did not show a benefit of routinely using rotational atherectomy in patients with moderately or severely calcified obstructive coronary artery disease: 240 patients with complex calcified coronary lesions were randomly assigned to rotational atherectomy followed by stenting versus no rotational atherectomy stenting. The atherectomy group had higher levels of late in-stent lumen loss at 9 months. In follow-up at 9 months postprocedure, rates of restenosis, TLR, definite stent thrombosis, and major adverse cardiac events were similar between the 2 groups before paclitaxel-eluting stent implantation.[16] In current clinical practice RA use is mainly reserved to uncrossable CAC stenosis or for bailout lesion preparation in case of incomplete balloon expansion.

Orbital Atherectomy

The orbital atherectomy (OA) system was first described in 2008 and its use was meant for peripheral arteries.[31] This technique was transported in coronary field. The OA system is composed of a diamond-encrusted eccentric crown at the distal end of a drive shaft, powered by a pneumatic console. The operator can directly control anterograde and retrograde movement of the crown and orbit speed (from 80,000–120,000 rpm). The crown is continuously infused by a lubricant solution (ViperSlide).

Unlike the RA burr, the OA crown has diamond chips on front and back, thus permitting anterograde and retrograde atheroablation, OA is capable of treating different CAC scenarios, unlike to RA that needs different burrs to obtain larger cross-sectional areas, OA enlarging orbit of crown movement at faster speed reaches the same target. With single OA 1.25-mm crown through a 6-Fr guiding catheter the operator can be effective on reference vessels up to 3.5 mm in diameter. The movement is slow and poking; it permits intermittent coronary blood flow around the burr and reduces the risk stalling/entrapment. Conversely, in OA, the motion is uniform, gradual and continuous, pausing in interest segments to enable atheroablation. In expert operators, tactile and also audible changes could be felt. We report in Figs. 1-3 an OCT guided PCI of LAD treated by OA.

The treatment time should not pass 30 seconds, in fact a sound alert can be heard after 25 seconds of nonstop treatment; the safety is guaranteed as shown in ORBIT I trial by rapid and continuous infusion of ViperSlide. In the ORBIT I trial we have 94% procedural success rate in 50 patients, on the other hand clinical complications included 2 in hospital myocardial infarctions (4%) and cumulative rates of MACE: 6 coronary dissections (12%) and 1 perforation, with no slow-flow/no-reflow.[32,33] ORBIT II study with 443 patients presenting de novo calcified plaque to treatment with OA, OA was associated with a 97.7% rate of successful stent delivery, a 98.8% rate of less

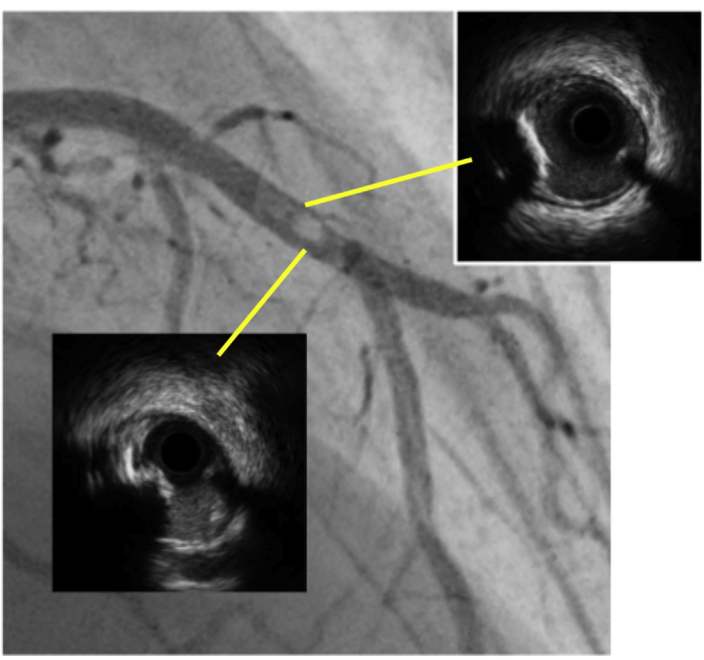

Fig. 1. Calcific nodule in mid LAD at coronary angiography and IVUS imaging.

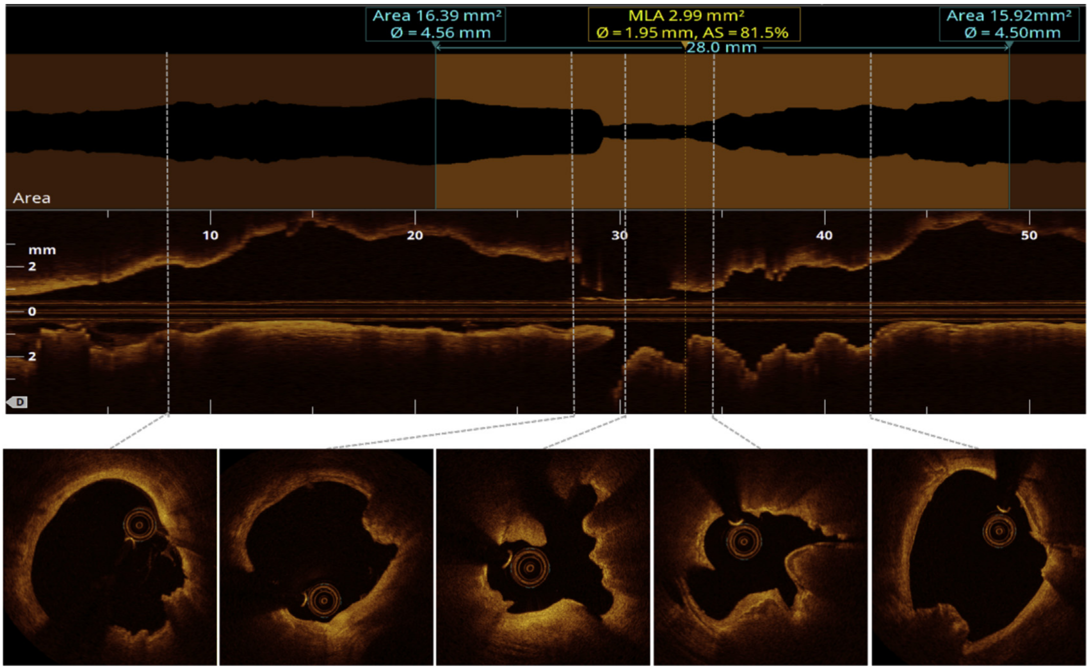

Fig. 2. OCT before OA.

than 50% stenosis post-PCI, and low rates of in-hospital Q-wave myocardial infarction (0.7%).[34–36]

Yamamoto and colleagues[37] found that in larger luminal area, OA led to a more radical plaque modification compared with RA, but in lesions with smaller lumen area, a similar degree of plaque modification occurred. Final stent expansion was similar, however Kini and colleagues[38] show a

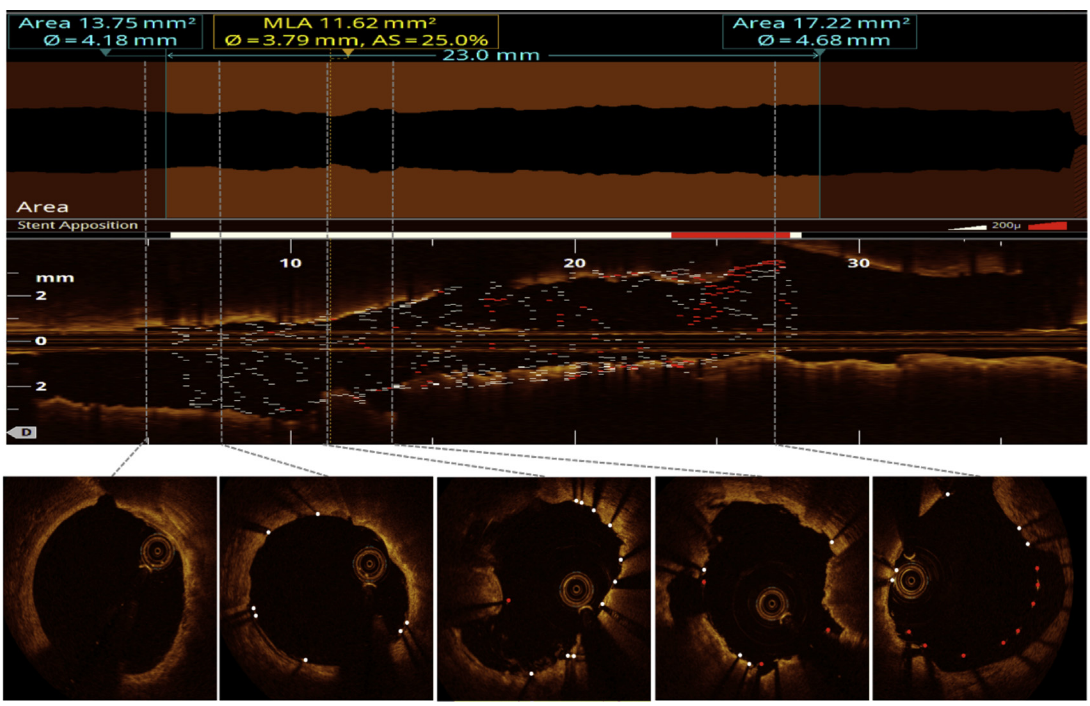

Fig. 3. OCT after OA and stent optimization.

better final stent apposition after OA. Orbital versus Rotational Atherectomy Effects On Coronary Microcirculation in PCI known as ORACLE (NCT03021577) will clarify another issue: the effect on microcirculation.

Excimer Laser Coronary Atherectomy

Laser was introduced for treatment of limbs ischemia[39] in 1980s, and was later supported for the use in coronary circulation.[40–43] Thanks to development of modern catheter and safe lasing techniques,[44,45] ELCA reached satisfying clinical outcomes.[46] The mechanics of ELCA are based on pulsed gas lasers, a mix of rare gas and a halogen element to generate short wavelength ultraviolet light (UVL): shorter is the wavelength, less deeper the penetration, less heat is produced and thus less traumatic for tissues. The principles of ELCA are 3: photochemical, photo-thermal, and photomechanical. UVL breaks carbon–carbon bonds, photochemical principle, elevating temperature of intracellular water and lead to rupture of cellular membrane and generating a bubble of vapor on the catheter tip, photothermal principle. At last, continuous formation and implosion of bubbles fragments the intravascular in a particulate of less than 10 μm diameter. The CVX-300 cardiovascular laser Excimer system (by Spectranetics, Colorado Springs, CO) uses Xenon chloride (XeCl) as the active medium. Operator personal safety devices should be carefully observed.

ELCA catheters are compatible with any standard 0.014-inch guidewire. Coronary catheters are available in four diameters (0.9, 1.4, 1.7, 2.0 mm) and those most commonly used have a concentric array of laser fibers at the tip.

Usually 0.9-mm × 80 catheter is used in fibrocalcific lesions thanks to its enhanced delivery and ability to emit laser energy at high power (80 mJ/mm^2) at the highest repletion rate (80 Hz). This is a situation where ELCA may be used, unless there are very significant calcification.[47,48] In highly fibrocalcific lesions, even for ELCA PCI more expert operators, the default choices remain RA or OA.

Efficacy of ELCA in PCI was achieved in 96.4% in ELLEMENT registry,[49] but careful case selection is mandatory successful procedures.

Shockwave Intravascular Lithotripsy

High-pressure balloon dilation and atherectomy may result inadequate to modify deeper calcium.

Coronary intravascular lithotripsy (IVL) with the Shockwave device (Shockwave Medical Inc., Santa Clara, CA), CE marked in 2017, is an innovative technique that can affect deeper calcium layer and alters calcium structure of plaque before stenting the lesion. Ali and colleagues[50] who studied 31 patients using OCT after IVL, firstly described this mechanism. The practice is borrowed on the well-known treatment strategy for renal calculi, used for decades to fragment kidney stones sparing soft tissues.

The Shockwave Medical coronary catheter is composed of a single-use catheter that contains multiple sonic emitters in a unique balloon, producing approximately 3 kV energy. The emitters create sonic pressure waves that spread uniformly and circumferentially. These waves can physically

Table 1
Treatment indications of coronary lesions with high calcium content before stenting and optimization

TECHNIQUES	NC BALLOON				CUTTING/SCORING BALLOON				ROTATIONAL ATHERECTOMY				ORBITAL ATHERECTOMY				ELCA				LITHOPLASTY BALLOON			
Characteristics / Lesion Types	Cr	UncL	OL	ULM	Cr	UncL	OL	ULM	Cr	UncL	OL	ULM	Cr	UncL	OL	ULM	Cr	UncL	OL	ULM	Cr	UncL	OL	ULM
Calcium Arc < 180° Calcium Lenght < 5 mm Calcium Thickness < 0.5 mm	Green	Red	Green	Green	Red	Red	Red	Red	Red	Yellow	Red	Red	Red	Yellow	Red	Red	Yellow	Green	Yellow	Red	Red	Red	Red	Red
Calcium Arc ≥ 180° Calcium Lenght < 5 mm Calcium Thickness < 0.5 mm	Yellow	Red	Yellow	Yellow	Yellow	Red	Red	Yellow	Red	Yellow	Red	Red	Red	Yellow	Red	Red	Yellow	Green	Yellow	Red	Yellow	Red	Yellow	Yellow
Calcium Arc ≥ 180° Calcium Lenght ≥ 5 mm Calcium Thickness < 0.5 mm	Yellow	Red	Yellow	Yellow	Yellow	Red	Red	Yellow	Yellow	Green	Yellow	Yellow	Yellow	Green	Red	Green	Yellow	Green	Yellow	Red	Green	Red	Green	Green
Calcium Arc ≥ 180° Calcium Lenght ≥ 5 mm Calcium Thickness ≥ 0.5 mm	Red	Red	Red	Red	Yellow	Red	Red	Yellow	Green	Green	Green	Green	Green	Green	Red	Green	Yellow	Green	Yellow	Red	Green	Red	Green	Green
Calcium Arc < 180° Calcium Lenght ≥ 5 mm Calcium Thickness ≥ 0.5 mm	Green	Red	Yellow	Yellow	Red	Red	Red	Red	Yellow	Yellow	Yellow	Yellow	Green	Green	Red	Green	Yellow	Green	Yellow	Red	Yellow	Red	Yellow	Yellow

Red: Generally not to be used; Yellow: To use after careful evaluation; Green: First line choice.

This table shows the technical advices to better face each calcific lesion type in different anatomical and pathological settings.

Abbreviations: Cr, Crossable lesion not involving ostium and with protected left main; OL, Ostial Lesions; ULM, Unprotected Left Main; UncL, Uncrossable Lesions.

fracture calcium, minimizing barotrauma attributable to low inflation pressure (4 atm).

Catheters available for this technique vary from 2.5 to 4.0 mm diameter and 12 mm in length, the generator delivers 10 pulses in sequence (1 pulse/s) till a maximum of 80 pulses per catheter.

Lithotripsy balloon is inflated to 405 kPa during, following pulsatile energy erogation.

Feasibility of intravascular lithotripsy for modification of severe coronary artery calcification was demonstrated in the Disrupt CAD I study (Disrupt Coronary Artery Disease).[51] After this, Disrupt CAD II was a prospective multicenter, single-arm post-approval study designed to assess the safety and performance of the Coronary IVL System to treat calcified stenotic coronary lesions.[52]

Patients had silent ischemia, unstable or stable angina with myocardial ischemia, or stabilized acute coronary syndrome without elevation in cardiac biomarkers, presenting a single target lesion requiring PCI with a diameter stenosis $\geq$50% and length $\leq$32 mm, in native coronary arteries.

The post-IVL luminal gain was 0.8 $\pm$ 0.5 mm and residual stenosis was 29% $\pm$ 12% with further decrease to 12% $\pm$ 5% following drug-eluting stent implantation.

No comparison data are available between atherectomy techniques and IVL, a retrospective review of 54 patients treated with IVL reported a higher incidence of isolated ventricular beats or asynchronous cardiac pacing during shockwave, not associated with clinical adverse events.[53]

WHAT'S NEXT TO HANDLE?

Lately technological advancements in PCI CAC equipment are consistent: resistant balloons that can reach very high pressures, sharp cutting and scoring devices, formidable burrs in RA and OA, modern balloon producing intense waves like in IVL and futuristic lasers. We can see even hybrid promising approaches to these lesions (RotaTripsy).[54] Particularly, IVL has a huge potential in concentric calcifications for its 3 main characteristics: safety, efficacy, and short learning curve.

We recently proposed a newer PCI algorithm based on imaging techniques, such as OCT and IVUS.[55] Based on our experience, calcium spread deeply but also longitudinally through the vessel wall, thus deeper calcified lesions should correspond to longer and more concentric involvement. This rationale permits to add an adjunctive point to the Fujino score for an arc greater than 270° and a length greater than 5 mm, thus directing the expert operator to the best procedure.

However, it is important to stay grounded in our everyday practice: coronaries anatomic and pathologic characteristics deeply impact on PCI planning, incomplete expansion and poor stent apposition, more frequent in calcified lesions, are predictive of target lesion failure and late stent thrombosis: calcium is a predictor of interventional treatment failure.[56]

We summarize in **Table 1** our PCI strategy in CAC.

Concluding, we always need to evaluate the stability of other vessels, even if they are not the principal aim of our work, evaluating completely the coronary tree and its balance. As is well known, each treatment should be tailored for patient and lesion characteristics.

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