

Cracking the Culprit Calcium in Coronaries

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ABSTRACT

Coronary artery calcium score, which is calculated by computed tomography (CT), is an independent predictor of adverse cardiac events in both symptomatic as well as asymptomatic patients. CT coronary angiography is growingly employed not only to evaluate the vessel stenosis, but also to characterise and quantify the extent and amount of coronary atherosclerosis. The four features of high-risk plaques on CT coronary angiography include napkin-ring sign, low CT attenuation, spotty calcification, and the remarkable positive remodelling. Spotty calcium is closely associated with unstable plaques and acute coronary syndrome. Managing patients

with calcified coronaries is a dilemma for the interventional cardiologists. Intravascular imaging, either an IVUS or OCT, is recommended in order to have a meticulous analysis of the severity and characterization of the plaque morphology as coronary angiography alone underestimates calcium and does not easily allow its quantification. Performing percutaneous coronary intervention on a heavily calcified coronary lesion poses several technical challenges. IVL is an up-and-coming new treatment modality for tackling coronary artery calcification. In the foreseeable future, this calcium-modification technique is likely to become the established strategy for dealing with challenging complex, calcified lesions.

Key words: Coronary calcification; Calcified coronaries; Calcium-modification; Rotablation; Atherectomy; Intravascular lithotripsy; IVL

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EDITORIAL

Coronary artery calcification (CAC) is considered to be a distinctive feature of atherosclerosis, a variant of an ectopic bone formation^[1]. Coronary artery calcium score, which is calculated by computed tomography (CT), is an independent predictor of adverse cardiac events in both symptomatic as well as asymptomatic patients, as described by Budoff et al. in the Multi - Ethnic Study of Atherosclerosis (MESA) study^[2].

There are two recognised types of coronary calcification; intimal and medial. Atherosclerotic calcification is seen to occur in the intima^[3]. It is thought that inflammatory mediators and elevated levels of lipid within the atherosclerotic lesions provoke osteogenic differentiation of vascular smooth muscle cells^[4]. On the other hand, medial calcification, also known as Monckeberg's sclerosis, is less prevalent in coronary arteries and is more often linked to advanced age, diabetes mellitus and chronic kidney disease^[5].

Computed tomographic coronary angiography (CTCA) and intracoronary imaging quantify plaque volume and macro-calcifications (calcium deposits > 200 mm), however, these modalities fail to detect micro-calcifications (calcium deposits < 50 mm). CTCA is not able to distinguish between intimal and medial calcification. Macro-calcifications are recognized as spotty and sheet calcifications; spotty calcification is considered to be a high-risk plaque. Micro-calcifications have been described in the fibrous cap of atherosclerotic plaques, where they may be linked to biomechanical instability^[6].

The impact of CAC on prognosis following percutaneous coronary intervention have been established in 16 randomized, controlled trials including a total of 23,481 patients with a mean follow-up of 18 months^[7]. The data demonstrated that severe coronary calcification resulted in sub-optimal revascularization (48% vs. 55.6%, $p < 0.001$), and was associated with significantly higher mortality (10.8% vs. 4.4%, $p < 0.001$), higher rate of death and myocardial infarction (23.2% vs. 10.9%, $p < 0.001$) and higher incidence of coronary revascularization (31.8% vs. 22.4%, $p < 0.001$)^[7].

CTCA is growingly used not only to assess the lesion stenosis but also to characterize and quantify the extent of coronary atherosclerosis. Measuring the CAC and coronary plaque burden on CTCA helps in predicting the atherosclerotic cardiovascular disease risk in the long-term. CTCA may play a role in visualizing coronary calcification, particularly for the detection of type I (ratio of calcified plaque volume to vessel circumference (RVTC $\leq 25\%$) and type II (RVTC 26-50%) calcified plaques, in contrast to type III (RVTC 51-75%) and type IV (RVTC 76-100%)^[8].

The four features of high-risk plaques on CTCA include napkin-ring sign, low CT attenuation, spotty calcification, and the remarkable positive remodelling. Spotty calcium is closely associated with unstable plaques and acute coronary syndrome. CTCA is considered to be an imperative tool for the procedural success during coronary intervention as it helps in recognizing and localizing the calcium in the coronary arteries^[9-12].

Intravascular imaging, either an IVUS or OCT, is recommended in order to have a meticulous analysis of the severity and characterization of the plaque morphology as coronary angiography alone underestimates calcium and does not easily allow its quantification.

IVUS is the most effective diagnostic tool to detect endo-luminal and deep calcium, but one of the major issues is that the leading edge of the endo-luminal calcium conceals in its shadow the actual mass of calcium in the vessel wall. On the other hand, optical coherence tomography (OCT) has a restricted depth penetration but can image superficial calcium and determine the back side of the calcified plaque, making the measurement of the total calcified mass possible^[13]. Delineating calcification in the vessel by using intracoronary imaging guides the interventionists in using the appropriate techniques for calcium-modification and lesion preparation prior to stent implantation.

Currently there is no proven medical therapy that can reverse coronary calcification. In St. Francis Heart Study^[14], 1005 asymptomatic, healthy men and women, age 50 to 70 years, with CAC score > 80th percentile for age and gender were randomized to atorvastatin 20 mg daily or placebo. Atorvastatin resulted in reduction of total cholesterol, low-density lipoprotein cholesterol and triglycerides but had no effect on the progression of coronary calcium score. The treatment also failed to show any significant decline in atherosclerotic cardiovascular disease events^[14].

Other treatments like calcium-channel blockers^[15], phosphate-

binders^[16,17] and hormone therapy^[18] have all been shown to reduce CAC progression in small randomized trials, however, these findings need to be confirmed in large-scale randomized trials.

The cornerstone of treatment is lifestyle modification, like smoking cessation, alcohol abstinence, weight loss, optimal control of blood pressure, blood sugar and lipid levels that may help to slow the progression of coronary calcification. In symptomatic patients with heavily calcified coronary arteries, complex coronary intervention or coronary artery bypass grafting may need to be considered^[19].

Managing patients with calcified coronaries is a dilemma for the interventionists. The severity of a calcified lesion is usually underestimated because the density of the calcium makes it incredibly difficult to assess the severity of the lesion meticulously. Performing percutaneous coronary intervention on a heavily calcified coronary lesion poses several challenges such as difficulty in passing the wire down the lesion, tracking the balloons and devices and dilating the lesion and are, furthermore, associated with significant risks and complications and unfavourable clinical outcomes.

The various calcium-modification interventional techniques currently available can be broadly divided into two groups: 1) techniques without using balloon or atherectomy; 2) techniques using balloon-based plaque rupture.

Among the techniques without using balloon include rotational atherectomy (RA), orbital atherectomy (OA) and Excimer laser coronary atherectomy (ELCA)^[20,21]. The procedures with devices based on techniques using balloon constitute super high-pressure non-compliant balloon, cutting/scoring balloon and intravascular lithotripsy (IVL).

RA fractures the calcified plaque efficiently by high-speed rotation of an elliptical diamond-tipped burr, which works judiciously on the calcium in the vessels and culminates in debulking of the plaque. RA has been in use for over three decades and was primarily developed to aid atherosclerotic plaque debulking but has eventually faded in view of the significant procedure-related complications and restenosis^[22]. After the inception of drug-eluting stents, interventionists started using RA again not for plaque debulking but for lesion preparation in order to facilitate balloon expansion and optimal stent apposition in cases of severe coronary calcification. Significant vessel dissection abutting acute closure, slow/no re-flow, peri-procedural myocardial infarction, athero-embolism and transient profound hypotension are the most commonly encountered risks associated with RA.

OA is an adjunctive technique which intends to prepare the heavily calcified lesion prior to stenting. Genereux and his colleagues^[23], in ORBIT II trial, recruited 443 patient with significant coronary calcification who underwent OA. They reported an impressive device success rate of 98.6% with residual stenosis of <50%. A 2-year follow-up demonstrated major adverse cardiovascular events (MACE) of 19.4% with target lesion revascularization (TLR) rate of 6.2%^[23]. The most notable complications associated with this technique include coronary dissection, slow-flow/no-reflow and coronary perforation.

IVL is an up-and-coming new treatment modality for tackling coronary artery calcification. The recent clinical trials^[24-26] support the efficacy of IVL in triggering circumferential fracture in heavily calcified plaques, resulting in significant luminal gain and paving the way for optimal stent expansion.

The IVL system is a single-use, disposable low-pressure balloon-based system that has two emitters, 6 mm apart, which transforms electrical energy into acoustic circumferential pulses emitting sonic waves safely breaking both superficial as well as deep calcium deposits within the arteries^[27,28].

IVL is unique in the way that it does not depend on mechanical tissue injury by physical interaction, seen in other techniques like atherectomy or cutting/ scoring balloon, but instead by a diffuse acoustic pulse through a balloon inflated at low pressure of 4 to 6 atm. By conveying shockwave energy locally, the effect of IVL is more marked with incremental severity of calcification. IVL causes circumferential plaque modification which leads to optimal stent apposition and expansion^[29].

The Disrupt CAD^[24], a prospective, multi-centre, single-arm, non-randomized study, enrolled 60 patients and used Shockwave IVL to pre-dilate significantly calcified coronary lesions. By using OCT, the authors displayed enhanced circumferential calcium fracture and luminal gain, with 98.3% device success (defined as precise device delivery and application of IVL to the target lesion) and 100% stent delivery. The study reported 95% freedom from MACE at 30-day and 92% at 6 months.

The Disrupt CAD II^[25], was a prospective, multicentre, single-arm study which aimed to assess the safety and effectiveness of intracoronary lithotripsy^[25]. The study recruited 120 patients over a period of 10 months. Severe calcification was reported in 94.2% of lesions (defined as calcification within the lesion on both sides of the vessel assessed by angiography)^[25]. IVL catheter was effectively delivered to all target lesions, and IVL was performed in all of the cases. Using OCT, calcium fracture was identified in 78.7% of lesions. The primary end point of in-hospital MACE [including cardiac death, MI, or target vessel revascularisation], occurred in 5.8% of patients, consisted of seven non-Q-wave myocardial infarctions. IVL was safely accomplished in 92.4% of the cases.

The Disrupt CAD III^[26] a prospective, single-arm multicentre trial, was designed to get regulatory approval of coronary IVL. The trial recruited 431 patients at 47 sites in 4 countries. Using OCT, calcium fractures were reported in 67.4% of lesions after IVL use. The procedural success (defined as successful stent delivery with a residual stenosis <50% by core laboratory assessment without in-hospital MACE) was reported as 92.4% and 30-day freedom from MACE (composite occurrence of cardiac death, MI, or target vessel revascularization [TVR]) was 92.2%.

IVL has been exceptionally safe and an indirect comparison to the rates of complications following high-pressure balloon dilatation, RA and OA, demonstrated a superior safety profile in dealing with heavily calcified stenotic lesions. Comparing to slow flow/no reflow seen in a contemporary series with RA^[30], slow flow/no reflow was not reported in any of the published studies and reports. IVL refrains from guidewire bias and enables symmetrical luminal gain, a phenomenon unrecognized in RA^[31].

In contradiction to RA or OA, which culminates in microfragments that embolize distally, resulting in impaired microcirculatory function^[32], larger fragments of calcium produced by IVL remain in-situ, thus having no effect on the microcirculatory function.

IVL has a number of advantages over atherectomy. There is no need for a specific training to use IVL due to the fact that the device is delivered synonymous to a standard catheter-based intervention. IVL is performed at low atmospheric balloon inflation, hence minimizing the trauma to the vessel. Furthermore, whilst treating a bifurcation lesion, with IVL, the side-branch protection utilizing a guide-wire may be carried out flowingly, without the risk of wire entrapment or severing, which may transpire with RA or OA.

In some complex, clinical scenarios, the two calcium-modification techniques, RA and IVL, may be used as complementary techniques. RA helps in modifying the intimal calcium and enable crossing

balloons/stents through heavily calcified lesions. However, in cases of significant circumferential deep calcium plaques, RA may not be adequate to procure optimal expansion of the devices. IVL is a fantastic tool to treat deep calcium plaques but its deliverability is limited due to its poor crossing profile. A hybrid approach, using a combination of these two techniques, known as Rota-Shock, may be conducive in treating severely calcified stenotic lesions.

As opposed to the ablation techniques, given that IVL is balloon-based, it is simple to use and the learning curve is not steep. In the foreseeable future, this calcium-modification technique is likely to become the established strategy for dealing with challenging complex, calcified lesions.

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