New Modalities of Treatment for Coronary Calcific Lesions

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Abstract

Keywords

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- imaging
- treatment

Since the publication of the previous article on the same topic in the journal, as a result of the better understanding in intravascular imaging (intravascular ultrasound [IVUS] and optical coherence tomography [OCT]) and introduction of intravascular lithotripsy (IVL) into clinical practice, the outcomes in patients with calcified coronary lesions have become more predictable and safe with lesser complication rates.

Introduction

Interventional treatment of heavily calcified lesions remains the Achilles heel of an interventional cardiology even today. Attempts at overcoming this challenge are fraught with a higher risk of immediate complications such as inability of the stent to cross, delamination of polymer, altered or improper drug elution, inadequate stent expansion and balloon rupture with occasional coronary perforations, as well as late failures due to stent underexpansion and malapposition, and consequent poor outcomes.¹ As many as 30 to 35% cases presenting with acute coronary syndromes have calcific coronary stenoses, making their management even more challenging.²

Since the original description of coronary “ossification” by Edward Jenner and Caleb Hillier, we have come a long way in understanding the pathogenesis and characterizing coronary calcium. Proper characterization of coronary calcium by multimodal imaging with subsequent optimal preparation of the lesion “bed” are essential prerequisites for success while treating a calcific lesion. The interventionist’s armamentarium is today well-equipped with a wide array of devices to tackle coronary calcium. This article will focus on the newest modalities available at our disposal as of now to tackle these lesions.

Pathophysiology of Calcified Plaque

The mechanism of coronary artery calcification differs considerably compared with peripheral arterial calcification. In peripheral arteries, calcification in media is usually mediated by osteoblast-like cells acting on a stimulus of changes in systemic calcium and phosphate homeostasis. Atherosclerotic intimal coronary calcification, on the contrary, is due to dysmorphic calcium deposition by chondrocyte-like cells for which the stimulus is inflammatory cytokines from tissue macrophages and foam cells. The key pathophysiological factor is likely to be inflammation that begets calcification which, in turn, begets more inflammation leading to a vicious cycle.

The initial lesions are foci of microcalcifications (which are only detected on histopathology) over areas ranging from 0.5 to 15 μ m in size. These areas of microcalcifications can fuse into larger masses to become speckles and calcified sheets, which are detected in vivo by CT or intravascular imaging. Large protruding subintimal masses may lead to plaque destabilization and thrombus formation and has been detected in 5% cases of unstable coronary syndrome and ST-elevation myocardial infarction (STEMI) (the calcific nodule). Statin therapy promotes replacement of the fibronectin core within a plaque by fibrocalcific tissue.^{3–7}

Coronary Calcium and Events

Coronary artery calcium score by CT was an independent predictor of coronary events irrespective of symptom status in the multi-ethnic study of atherosclerosis (MESA) study of 10-year follow-up. The SYNTAX score, a method to quantify the complexity of coronary lesions, also places high importance to the presence of heavy calcification (which is given 2 pts per lesion). Severity of calcification is greater with advanced age, hypertension, dyslipidemia, diabetes, and chronic kidney disease.^{8,9}

Assessment of Coronary Calcium

CT Coronary Artery Calcium (CAC) Score

Formal calcium scoring was introduced in 1990 and has proven to be simple, elegant, reliable reproducible tool in predicting adverse outcomes. Agatston score was originally proposed for electron beam CT but was later adopted to multidetector CT using 120 KVP with variable mA and 2.5 mm slice thickness. It is totaled score of all calcified lesions and all total calcified areas and maximum calcium density (> 130 HU). Other scores are volume score and mass score. They are upwardly weighted with calcium density and fail to capture regional distribution of calcium with no account of number or size of calcified lesions. A score which accounts for calcium density and regional distribution, focal versus diffuse, number of lesions, lesion size, and microcalcification will refine the predictability. Some CAC features may be protective against the risk of atherosclerosis. In the MESA study, there was an inverse association between CAC density and cardiovascular disease (CVD) outcomes.^{10,11}

The ability to detect vulnerable plaque by CT is limited. In the ICONIC nested case control arm of the CONFIRM registry (189 pts in each group), 1 k plaque (1000 Hu) is associated with lower risk of future acute coronary syndrome (ACS) during a follow-up period of around 3.9 years.¹²

Fluoroscopy–Coronary Angiography

Coronary calcification could be present in 8 to 32% patients undergoing coronary intervention. Coronary angiography

often underestimates calcium severity and depth of calcium within the plaque. Radiopacity observed only during the cardiac cycle before injection of contrast medium is considered moderate by angiography. Radiopacity observed without cardiac motion, visible on both sides of the arterial lumen, as a double track (tram track calcification) is considered severe angiographically. Sensitivity of fluoroscopy for calcium detection is 40.2%, intravascular ultrasound (IVUS) 82.7%, and optical coherence tomography (OCT) 76.8% in one study.¹² Culprit lesion calcification was severe in 402 patients (5.9%), moderate in 1,788 (26.1%), and none/mild in 4,665 (68.1%) patients of ACS.²

Noninvasive assessment of coronary calcification like fluoroscopy and CT scan are suboptimal in guiding treatment modalities. IVUS can give idea of the arc and length of calcium but does not measure thickness of calcium correctly (due to acoustic shadowing). OCT gives better information of calcium distribution. Fugino has proposed a scoring system for OCT, which can aid in device selection for lesion preparation. Two points for maximum angle > 180°, 1 point for maximum thickness > 0.5 mm, and 1 point for length > 5 mm. A lesion score of 4 was associated with poor stent expansion.¹³

The advantages and limitations of various modalities of delineating coronary calcium are depicted in ►Table 1.

Statins and CAC

Several randomized trials have shown that statins, despite being beneficial in preventing CVD events, were associated with progression of CAC. Volume of CAC is lessened, but density has increased with higher Agatston score, as higher weightage was given to density. There was a reduction in plaque volume and increase in calcium density by IVUS. Patients with gain of function mutation in PCSK-9 gene have extensive CAC and high prevalence of coronary artery disease (CAD). PCSK 9 inhibitors have no effect on CAC. Puri et al assessed plaque volume and calcification by IVUS in patients receiving high-dose statin, low-dose statin and no-statin therapy, and found that statins may stabilize plaques by calcifying necrotic core with reduction in coronary events.¹⁴ Consequently, the CAC score calculated by CT might be an imprecise modality in prognosticating patients on statins.

Table 1 Imaging techniques for coronary calcium detection: pros and cons

Diagnostic accuracy	Angiography	IVUS	OCT
Severe calcification	+++	+++	+++
Mild/moderate calcification	+	++	+++
Deep calcium	+	+++	++
Calcium arch	–	+++	+++
Calcium thickness	–	–	+++
Longitudinal calcium length	–	+	+++
Nonhomogenous plaque/necrotic core	–	+++	+
+++; Optimal ++; Moderate +; Modest			

Abbreviations: IVUS, intravascular ultrasound; OCT, optical coherence tomography.

Strategies to Tackle Calcified Coronary Lesions

“Failing to prepare is preparing to fail” - John Wooden

The choice of access site depends on the experience and comfort of the operator. Many centers (including ours) have today shifted to an exclusive radial first approach, while some still swear by femoral access. Success in tackling a calcified lesion depends hugely upon planning the approach and strategies. The choice of guide, wires, balloons, and other specialized hardware like guide extensions, buddy wire, anchor balloon contributes a great deal toward success or failure. There are many specialized devices available today to tackle calcified lesions, which can be broadly classified as ablation techniques (rotational/orbital atherectomy), balloon-based techniques (cutting/scoring balloon, super high pressure balloon), excimer laser and lithotripsy balloon. Of these, those which are available at our disposal for routine clinical practice as of today are discussed here.

High and Very High Pressure Noncompliant Balloons

“When in doubt, use brute force” - Ken Thompson

Noncompliant (NC) balloons are characterized by a resilience to tolerate high inflation pressures with just a small increase in their diameter. This property allows the use of higher pressures in a focal segment of a coronary without risk of dog-boning and subsequent complications like dissection and perforation. These are of maximum benefit in calcific lesions, where the calcium arc is $< 90^\circ$ and hence form the first choice in such cases.

The OPN NC balloon (SIS medical) is a unique super high pressure balloon that is 0.014" wire, 5F guide compatible, twin layer taper tip design with a rated burst pressure of 35 atm, linear compliance at > 40 atm, and available in sizes of 1.5 to 4.5 mm (0.5 mm increments) and three lengths (10, 15 and 20 mm).

In a multicenter, retrospective observational study of 326 consecutive undilatable lesions (with NC balloons) in patients involving two groups (group 1 < 40 atm, group 2 > 40 atm inflation pressure), Secco et al found that > 40 atm pressure was required in 46.9% pts. OPN balloon alone was adequate in 288 pts (90.5%). Rotablator was used in 17.3% in group 1 pts versus 1.5% in group 2. Coronary perforation occurred in 3 pts (0.9%) all in very high pressure (> 40 atm) group prior to stenting without rupture of balloon. At mean follow-up of 14 months, net event free survival was 91.5%, mortality of 1%, and target lesion revascularization (TVR) of 6.4%.¹⁵

Rotational Atherectomy

Rotational atherectomy (RA) system (Boston Scientific, Marlborough, Massachusetts) has a high-speed, rotating, elliptical, diamond-coated burr that acts as an abrasive on calcific plaque. Available sizes of the metallic burr are from 1.25 to 2.5 mm in increments of 0.25 mm. The burr is mounted over an advancer (RotaLink) driveshaft and connected to an external motor that converts compressed gas into rotational energy.

The Rota burr requires a dedicated 0.009-inch wire (Rotawire), which is flexible with minimal unfavorable wire bias. RA works on the principle of differential cutting—it preferentially ablates the fibrocalcific plaque tissue while sparing the compliant elastic tissue. The tissue is pulverized into 5 to 10 μ m (about the size of an RBC) debris, which are released into distal microcirculation and can lead to slow flow phenomenon in as many as 20% cases in one series.

The recommended burr/artery ratio is 0.5:0.6, and a safe range of burr revolution speed is between 135,000 and 180,000 rpm. The major factors influencing the outcome after RA are the eccentricity of calcium, luminal area, burr size, and degree of guide wire bias. Complications of RA include burr entrapment, coronary dissection, perforation and transient atrioventricular block (especially with right coronary RA). The risks of atrioventricular block can be mitigated with the insertion of a temporary pacemaker or pharmacologically with aminophylline or atropine administration. With experience, the incidence of complications can be minimized. Avoiding lesions in tortuosity, allowing for adequate time between runs, and preventing burr deceleration > 5000 rpm can reduce complications.¹⁶⁻²¹

Cutting and Scoring Balloons

The first cutting balloon (Flextome Cutting Balloon) was introduced in 1991 by Boston Scientific and was available in monorail or over-the-wire catheter. It consists of a NC balloon with a set of 3 micro blade longitudinally oriented on the surface, which produces incisions within the atherosclerotic plaque during balloon inflation. The microblades work by causing radial incisions on the media, which is presumed to reduce elastic recoil and neointimal proliferation. The microblades prevent balloon slipping, which is of advantage in cases of in-stent restenosis due to intimal hyperplasia. A cutting balloon has the dual advantages of a more controlled lesion pre dilatation at lower inflation pressure. The GLOBAL study failed to show superiority of cutting balloons over regular NC balloons in type A/B lesions and hence their usage has been limited to cases with severe calcification and in-stent restenosis. The new iteration with Wolverine technology is supposed to reduce the profile of cutting balloon.

Difficulty in crossing and tracking severely calcific lesions are considered frequent limitations of cutting balloons. The trackability of a cutting balloon maybe improved by a new generation of low-profile semicompliant balloons with a scoring element on the surface (AngioSculpt, Biotronik; Scoreflex, OrbusNeich; NSE Alpha, B Braun). Scoring balloons allow focal concentration of the force during inflation and decreases the chance of balloon slippage. The radial force during balloon inflation is mainly exerted on the scoring element, which is transmitted in turn to the vessel wall, leading to incisions in the atherosclerotic plaque. Prolonged inflation of a scoring balloon produces a distortion force capable of expanding a resistant calcified lesion, the so-called “creep phenomenon,” which helps achieve adequate dilatation of severely calcified lesions.²² The nitinol element ensures balloon anchoring with a lower risk of “melon-seeding,”

dissection and perforation. Scoring balloons are more flexible compared with cutting balloons, have a better profile, and can achieve full expansion with a low-inflation pressure, which reduces the trauma to the vessel wall and minimizes the risk of coronary dissection.²²⁻³¹ **Fig. 1** shows the results of AngioSculpt in a calcific left anterior descending (LAD) artery lesion.

Orbital Atherectomy (OA)

It is a relatively newer treatment for management of coronary lesions with severe calcification. Similar to RA, it consists of a diamond coated 1.25 mm crown; however, contrary to RA burr, the OA crown is eccentrically mounted and is coated with diamond chips on both front and back, which permits bidirectional ablation with burr advancement and withdrawal. On account of this, entrapment of an OA burr is much less likely. The crown is advanced over a 0.012-inch wire (Viper wire), which has better maneuverability than the Rotawire.^{19,32,33}

Centrifugal force generated during rotation pushes and compresses the crown against the plaque with a “sanding” action of the calcified component. Theoretically, OA might have a selective action on the rigid calcified part of the coronary, while the healthy compliant tissue might flex away and be spared. The size of the debris generated during OA is smaller (2 μ m), thereby making the chance of developing slow flow very minimal. When compared with rotablation, better plaque/lesion modification is associated with OA by producing deeper and longer cuts. True “ablation” of calcium component on OCT has been reported more frequently with OA than with rotablation.

OA was FDA approved in 2013. Diamondback 360 coronary orbital atherectomy system (Cardiovascular systems, Saint Paul, MN, USA) has single burr of 1.25 mm with two speeds of 80,000 and 120,000 RPM and Glide assist at 5000 RPM, mounted on Viper wire 0.012” with 0.014” tip, with classic and mini crowns. It is used with Viperslide lubricant and is 6F compatible. High-speed option is to be avoided in tortuous lesions and vessel diameter less than 3 mm. A minimum of 10 mm distance should be maintained between wire tip and crown. Minicrown has diamond-coated tip: useful in ostial or near occlusive lesions. Complications are akin to that of RA, although burr entrapment is rare. Angiographic complications occur in less than 1%. Minicrown was evaluated

in a multicenter coronary orbital atherectomy system trial (COAST) trial of 100 pts. ORBIT I FIM feasibility trial of 50 pts: prospective, nonrandomized in two sites in India (**Table 2**). Q3 Device success 98% and procedure success 94%. Comparison with Rotablation: small retrospective or observational studies. Safety and efficacy was established in ORBIT II trial. One study is ongoing: comparison of orbital versus rotational atherectomy effects on coronary microcirculation (ORACLE), which will determine their effect on coronary microcirculation.

Eclipse multicenter trial of 2000 pts compares OA with balloon angioplasty. Results are expected in 2022.³³

Intravascular Lithotripsy (IVL)

IVL is the latest addition to the toolkit against calcific coronary lesions which received a CE mark certification in May 2017 and was established on the principles of renal stone therapy. Sonic pressure waves preferentially impact hard tissues, disrupt calcium, and leave soft tissues undisturbed. Miniaturized and arrayed lithotripsy emitters create a localized field effect by converting electrical energy into transient acoustic pressure pulses at the site of calcium.

The IVL system (Shockwave Medical) is made up of three parts (**Fig. 2**): 1) IVL generator: portable and rechargeable, no external connections, quick and easy setup, 2) IVL connector cable: simple magnetic connections, push button activation, and 3) IVL catheter: mounted on workhorse 0.014” guide wire, monorail (RX). The mechanism of action of IVL, as described by Ali et al using OCT, was shown to be an enlargement of the lumen and single or multiple calcium fractures.

The IVL procedure is akin to standard angioplasty requiring minimal or nil learning curve. The shockwave balloon must be sized according to the reference vessel diameter (ratio 1:1). The steps are as follows:

1. IVL catheter crosses the calcific lesion. Integrated balloon positioned across area of interest and expanded to 4 atm to ensure apposition.
2. Electrical discharge from the emitters vaporizes fluid within the balloon, creating a rapidly expanding and collapsing bubble which generates sonic waves.
3. Waves create an unfocused, circumferential, localized field effect which selectively cracks intimal and medial calcium
4. Balloon can further be inflated to 6 atm (nominal pressure) to optimize lumen gain

Balloon: 12 mm IVL 4 atm, nominal 6 atm, rated 10 atm. Two emitters. one pulse per sec. 80 pulses per catheter

Shockwave C2: Balloon diameters: 2.5, 2.75, 3.0, 3.25, 3.5, 3.75, 4.0 mm. 6F guide compatible, crossing profile 0.043 to 0.046 inches. Energy: 3kV. Pressure: 50 atm. Depth of penetration: 3 mm.^{34,35}

As the shockwave catheter has a higher profile than conventional balloons, predilatation with standard balloons might be necessary in 40 to 45% of lesions. Plaque modification devices like cutting/scoring balloons/RA/OA can be used concomitantly as adjuvants in challenging cases. Currently, the use of IVL is limited to unstable and stable angina. IVL

Fig. 1 Post (A) and Pre (B) AngioSculpt 2.5 mm dilatation in pro left anterior descending (LAD) artery with Agatston score of 208 in LAD (total of 1000)

Table 2 Studies of orbital atherectomy

	ORBIT I	ORBIT II	REAL WORLD REGISTRY
No of pts	50	443	458
In-hospital MACE	4	9.8	–
1-year MACE	–	9.7	1.8
1-year TVR	–	5.9	7.5

Abbreviations: MACE, major adverse cardiac events; TVR, target lesion revascularization.

Fig. 2 Intravascular lithotripsy (IVL) system. IVL Generator, connector cable and IVL balloon catheter with 2 emitters

has also been during primary percutaneous transluminal coronary angioplasty (PTCA).³⁶ In patients with underexpanded stents due to heavy calcification, the circumferential sonic waves generated by the IVL system have the potential to extend beyond the stent struts and fracture deeper calcium deposits, which may aid in optimal stent expansion and opposition while lowering the complications that may be associated with other methods (►Fig. 3).

Electric signals mimicking pacing spikes on the electrocardiogram (ECG) tracing during pulse-delivery have been described. These so-called “shocktopics” and asynchronous cardiac pacing have been reported in a significant number of patients in up to 77.8% of the cases, with a 16-fold increased frequency at heart rate < 65 BPM. This VOO pacing may be proarrhythmogenic (risk of R on T phenomenon), and in patients with pacemakers, an eye needs to be kept on pacemaker function, which should be assessed postprocedure, and inappropriate sensing during the IVL cycles.^{37,38} IVL can trigger supraventricular arrhythmias or paroxysmal atrial fibrillation in susceptible patients undergoing right coronary artery intervention.³⁹ There are anecdotal reports of coronary perforation with the use of IVL.^{40,41}

IVL is to be used with caution in critical lesions and in very tortuous vessels. In vessel size > 4 mm or eccentric calcium plaques which prevent appropriate IVL balloon apposition to vessel wall, the success of IVL decreases and other options need to be explored. There are anecdotal reports of its use in unprotected left main disease.^{42,43} Rotatripsy is a hybrid drill and disrupt technique.^{44–46} IVL may also be useful in recalcitrant de novo lesions and in in-stent restenosis.⁴⁷

Clinical Evidence with IVL System

Disrupt CAD I and II are published. Disrupt III and IV are ongoing. The findings of DISRUPT CAD are summarized in ►Table 3.^{48,49}

We need large trials and long-term data with IVL before it is incorporated into routine practice.

Excimer Laser

Although introduced more than two decades ago, its role is presently very limited and is based on the principle of photoablation of atherosclerotic plaque. Laser produces ablation by way of mainly three main mechanisms: 1) photochemical (breaking molecular bonds), 2) photothermal, and 3) photomechanical. When laser acts upon a liquid medium (saline, contrast dye, blood) leading to release of expanding and exploding bubbles that press over the plaque, photomechanical ablation occurs. However, increasing proportions of calcium in a lesion seem to reduce the efficacy of laser. As a result, laser is not advised as the first-line therapy for lesions with severe calcification.^{50–52} The clinical use of coronary laser is limited to being a “bail-out strategy” in uncrossable/undilatable lesions and underexpanded stents.⁵³

The CVX 300 System (Philips) uses xenon chloride to produce a light emitted in the ultraviolet B spectrum (308 nm) with a penetration depth of 30 to 50 µm. A combination of excimer laser and RA was recently described (the RASER technique).⁵⁴

The various modalities for treatment of calcified lesions are summarized in ►Table 4.

Conclusion

Armed with the latest advances in the field, interventionalists are approaching calcific lesions today with greater confidence and renewed enthusiasm. The success rates are rising, and complication rates are falling, signaling the onset of a new and exciting era in the management of these hitherto seemingly impossible lesions. Newer generation drug-eluting stents (DES) and more effective antiplatelet agents have greatly reduced the risk of stent thrombosis and restenosis. In clinical practice, we come across a lot of physician inertia and financial constraints because of which most of the dedicated devices to tackle coronary calcium, especially RA, OA and IVL, are grossly underutilized.

IVL is a new and exciting technology that holds great promise for the future. It has a shorter learning curve and

virtually nonexistent complications compared with RA/OA and is currently only being hindered from becoming mainstream due to its cost which is currently proving to be almost prohibitive. Sometimes complex lesions may warrant the use of more than one technique to overcome the calcium (►Fig. 4).

The use of imaging (OCT > IVUS) helps to characterize the calcium and plan the strategy better. It is imperative to remember that a well-planned approach is a job half done. The IVUS/OCT score by Fujino et al helps decide the choice of initial therapy. Lower scores (1–2 points) can go for high or very high pressure balloons, whereas high scores (3–5 points) are better served by IVL. One of the most challenging aspects of planning treatment modalities is that most of the imaging modalities we are dependent on are invasive in nature and hence often throw up surprises while evaluation on table, prompting a change in strategy during procedure. The availability of an accurate noninvasive modality for evaluation of calcific lesions will greatly change the way we approach these lesions in the future.

As healthcare scales newer heights and longevity increases, the problem of calcific coronary stenoses is likely to be encountered by interventionalists with an increasing frequency in the future when dealing with an aging population with multiple comorbidities like diabetes and renal failure. It is essential to be well-versed with the various strategies to tackle these lesions and train ourselves with imaging techniques that will form the basis of lesion assessment and planning. The acronym ROLE (Rotablator, OA, IVL and

Fig. 3 Use of IVL for underexpanded stent in right coronary artery (RCA), pre (A) and post (B)

Table 3 The DISRUPT CAD studies

Disrupt CAD I	<i>N</i> = 60	Feasibility study	Success 94%, MACE 5.8%
Disrupt CAD II	<i>N</i> = 120	Safety, efficacy study	Success 94.2% 1-month MACE 5.8%, non Q MI.
Disrupt CD II, OCT substudy	47	Mechanism of benefit	Intraplaque ca fracture 78.7%, 3.4+/□2.6 per lesion
Disrupt CAD III	<i>N</i> = 392	Ongoing, USA, Europe	For FDA approval
Disrupt CAD IV	<i>N</i> = 72	Ongoing, Japan	Results 2022

Table 4 Summary of commonly used treatment modalities for tackling calcified coronary lesions

Modality	Types	Advantages	Disadvantages	Evidence
Scoring balloon	Angiosculpt NSE α Scoreflex	Easy to use, controlled calcium disruption	High crossing profile, not useful in high calcium burden	Meta-analysis
Cutting balloon	Flextome	Controlled cutting	High crossing profile	Meta-analysis
RA	Boston Rota wire	Effective, forward, pulverization	Higher complications, no side branch protection	Rotaxus
OA	Spectranetics, Philips, Viper wire	Forward and backward sanding	Higher complication, no side branch access	Orbit 2
IVL	Shockwave	Controlled Ca rupture in plaque	Preserved side branch access	Disrupt CAD I and II
Excimer laser	Philips, spectranetics	Unexpanded stents, ISR		Element registry LARS registry

Abbreviations: ISR, in-stent restenosis; IVL, **intravascular lithotripsy**; OA, orbital atherectomy; RA, rotational atherectomy.

Fig. 4 Patient with a calcific lesion in mid left anterior descending (LAD) artery (yellow arrow, **A**) as seen on intravascular ultrasound (IVUS) (**B**), rotablator with 1.25 mm burr done (**C**), after rota IVUS (**D**) showed that the calcium failed to yield. Cutting balloon inflation with Angiosculpt was done (**E**) after which the calcium yielded (**F**). Final result (**G**, **H**)

Excimer laser) should be recalled in highly calcified coronary lesions. IVL is a transformational therapy, which with its short learning curve and safety even in the hands of relatively inexperienced operators, holds great promise for the future. One can only hope that with increasing use, costs decrease and give this wonderful therapy the spot in the limelight that it truly deserves.

Conflicts of Interest

None declared.

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