

Safety, efficacy, and optical coherence tomography insights into intravascular lithotripsy for the modification of non-eruptive calcified nodules: A prospective observational study

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Abstract

Background: Non-eruptive calcium nodules (CNs) are commonly seen in heavily calcified coronary artery disease. They are the most difficult subset for modification, and may result in stent damage, malapposition and under-expansion. There are only limited options available for non-eruptive CN modification. Intravascular lithotripsy (IVL) is being explored as a potentially safe and effective modality in these lesions.

Aims: This study aimed to investigate the safety and efficacy of the use of IVL for the modification of non-eruptive CNs. The study also explored the OCT features of calcium nodule modification by IVL.

Methods: This is a single-center, prospective, observational study in which patients with angiographic heavy calcification and non-eruptive CN on OCT and undergoing PCI were enrolled. The primary safety endpoint was freedom from perforation, no-reflow/slow flow, flow-limiting dissection after IVL therapy, and major adverse cardiac events (MACE) during hospitalization and at 30 days. MACE was defined as a composite of cardiac death, myocardial infarction (MI), and ischemia-driven target lesion revascularization (TLR). The primary efficacy endpoint was procedural success, defined as residual diameter stenosis of <30% on angiography and stent expansion of more than 80% as assessed by OCT.

Results: A total of 21 patients with 54 non-eruptive CNs undergoing PCI were prospectively enrolled in the study. Before IVL, OCT revealed a mean calcium score

Abbreviations: ACS, Acute Coronary Syndrome; AI, Asymmetric index; ARC, Academic Research Consortium; CCS, Chronic Coronary Syndrome; CN, Calcified Nodule; EI, Eccentricity Index; IVL, Intravascular Lithotripsy; IVUS, Intravascular Ultrasound; MACE, Major Adverse Cardiovascular Event; MLA, Minimal Lumen Area; MSA, Minimum Stent Area; OCT, Optical Coherence Tomography; PCI, Percutaneous Coronary Intervention.

This study demonstrates short-term safety and efficacy and provides unique OCT insights into the modification of non-eruptive calcified nodules by intravascular lithotripsy.

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of 3.7 ± 0.5 and a mean MLA at CN of $3.9 \pm 2.1 \text{ mm}^2$. Following IVL, OCT revealed calcium fractures in 40 out of 54 (74.1%) CNs with an average of 1.05 ± 0.72 fractures per CN. Fractures were predominantly observed at the base of the CN (80%). Post IVL, the mean MLA at CN increased to $4.9 \pm 2.3 \text{ mm}^2$. After PCI, the mean MSA at the CN was $7.9 \pm 2.5 \text{ mm}^2$. Optimal stent expansion (stent expansion $>80\%$) at the CN was achieved in 85.71% of patients. All patients remained free from MACE during hospitalization and at the 30-day follow-up. At 1-year follow-up, all-cause death had occurred in 3 (14.3%) patients.

Conclusions: This single-arm study demonstrated the safety, efficacy, and utility of the IVL in a subset of patients with non-eruptive calcified nodules. In this study, minimal procedural complications, excellent lesion modifications, and favorable 30-day and 1-year outcomes were observed.

KEYWORDS

calcified nodule, intravascular lithotripsy, non-eruptive calcified nodule, optical coherence tomography, percutaneous coronary intervention

1 | INTRODUCTION

Calcified nodules (CN) are dense, eccentric nodular calcifications seen protruding into the lumen of coronary arteries. CNs can either be eruptive or non-eruptive. Eruptive CNs have been recognized as a cause of acute coronary syndrome (ACS), observed in 2%–8% of patients.¹ The presence of non-eruptive CNs has historically been underestimated, yet their importance becomes more pronounced with advancing age, renal dysfunction, and the severity of calcification within the affected artery. In heavily calcified arteries, CNs can be observed in 43.5%–48.5% of lesions.^{2,3} Non-eruptive CNs limit device delivery, can damage stent struts & their polymer and may result in stent mal-apposition and under-expansion.²⁻⁴

Coronary angiography has a poor sensitivity for the quantification and distribution of calcium in coronary lesions.⁵ Hence, intra-coronary imaging plays a pivotal role in assessing calcified coronary lesions, particularly CNs. Upon identification of a CN, modification remains a challenge and is usually performed either with modified balloons, atherectomy devices, or lithotripsy. While modified balloons (high-pressure balloons, cutting, and scoring balloons) can be used for lesions with less calcium burden, their role in CN modification is limited as an adjunctive therapy due to their eccentricity and risk of rupture at the site opposite to the nodule. Rotational atherectomy on the other hand is a viable option for CN modification, but it suffers from wire bias. Orbital atherectomy (OA) seems to be an effective option for CN modification, but its evidence is limited only to case reports.^{6,7}

Intravascular lithotripsy (IVL) is both safe and effective for modification of severely calcified coronary artery disease.⁸⁻¹¹ Its role in modifying CNs is recently being explored with encouraging results.¹² This study aimed to investigate the safety, efficacy, and insights provided by OCT regarding the use of IVL for the modification of non-eruptive CNs.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a single-center, prospective, observational study conducted at the Department of Cardiology, Army Institute of Cardiothoracic Sciences (AICT), Pune, India. The study complied with the provisions of the Declaration of Helsinki and was approved by the institutional ethics committee of our institution. Before enrollment, all patients provided written informed consent.

2.2 | Procedure

Consecutive patients presenting with angiographically apparent heavy calcification and non-eruptive CN as identified by OCT and undergoing PCI were enrolled for this study. Heavy calcification was defined as radiopacities noted without cardiac motion before contrast injection, generally compromising both sides of the arterial lumen, in vessels $\geq 1.5 \text{ mm}$ in diameter with $>50\%$ diameter stenosis. Non-eruptive CN was defined on OCT as a convex-shaped segment of calcification protruding into the lumen of the coronary artery with an intact stable intimal layer.

The Shockwave Medical Coronary Rx Intravascular lithotripsy System (Shockwave Medical Inc, Fremont, CA) was used for CN modification in the study. IVL was sized 1:1 with the reference diameter of the target vessel to allow for apposition with the vessel wall. It was taken across the calcified lesion and connected with a pulse generator via a connector followed by inflation with a mixture of saline with contrast (in 50/50 ratio) to a sub-nominal pressure of 4 atm. Each catheter emits a total of 80 shockwave pulses in eight cycles (10 pulses in each cycle at a frequency of 1

pulse/second). At the end of each cycle, inflation pressure is increased to 6 atm (nominal pressure) followed by deflation of the balloon to allow distal perfusion and dissipate heat. Pre-dilatation with a non-compliant or a semi-compliant balloon at the calcified lesion was done before IVL if the IVL balloon did not cross the calcified lesion. The number of IVL cycles per lesion was left to the operator's discretion guided by the calcified lesion morphology. OCT was performed before IVL, after IVL, and after stent implantation. OCT parameters studied include pre-IVL minimum lumen area (MLA), calcium (Ca) score,¹³ calcium arc concerning CN, number of CNs, proximal and distal reference diameter, post IVL gain in MLA at CN, calcium fracture (defined as gap created within calcifications after IVL therapy¹⁴) and its site on CN, dissection, post-PCI minimum stent area (MSA) at CN, stent expansion at CN, stent apposition, edge dissection, asymmetric index and eccentricity index at CN. Asymmetric index (AI) was calculated as $(1 - \text{minimum}/\text{maximum stent diameter})$ with a value <0.3 being considered as symmetrical stent expansion.² Eccentricity index (EI) was calculated as $\text{minimum stent diameter}/\text{maximum stent diameter}$ at the cross-section of MSA in the calcified nodule after stent placement.¹⁵ An EI >0.7 was classified as concentric while a value <0.7 was deemed as eccentric. Stent expansion at CN was calculated as $\text{Minimum stent area (MSA)}/\text{Average of Proximal and Distal Reference Lumen Area} \times 100$. Optimal stent expansion was defined as stent expansion $>80\%$. For the assessment of the Base and Apex of the calcium nodule, the calcium nodule was assessed at an OCT cross-section/frame where its peak elevation was maximal. The lower one-third of the calcium nodule was demarcated as the base, while the upper two-third was designated as the apex. For the convenience of the readers we have added a figure in the supplement illustrating this (Figure S1).

Thereby, all angiographic and OCT images were reviewed and analyzed by two independent cardiologists (interventional cardiologists with experience in OCT interpretation for >5 years) who were blinded to the clinical information. In cases of disagreement, the opinion of a third independent cardiologist was requested, and the final decision was obtained by consensus.

2.3 | Study endpoints

The primary safety endpoint was freedom from perforation, no-reflow/slow flow, flow-limiting dissection after IVL therapy, and major adverse cardiac events (MACE) during hospitalization and at 30 days. MACE was defined as a composite of cardiac death, myocardial infarction (MI), and ischemia-driven target lesion revascularization (TLR). The primary efficacy endpoint was procedural success, defined as residual diameter stenosis of $<30\%$ on angiography and stent expansion of more than 80% as assessed by OCT. Secondary individual endpoints were the occurrence of stent thrombosis (ST), cardiac death, MI, and or TLR. Cardiac death, MI, and TLR were defined as per ARC II criteria.¹⁶

2.4 | Follow-up

All patients were followed up in person at an out-patient clinic of the Army Institute of Cardiothoracic Sciences (AICT), Pune, India at 1 month and there after every 3 months till 1-year. No patients were lost to follow up.

2.5 | Statistical analysis

The categorical variables were expressed as percentages, the continuous variables were expressed as mean \pm standard deviation. Categorical variables were compared using the chi-square test/fisher exact test as applicable. Continuous variables were compared using the student t-test/Mann-Whitney U test as applicable. All two sided p-values less than 0.05 were taken as statistically significant. All Statistical analysis was performed using IBM SPSS version 24.0.

3 | RESULTS

A total of 21 patients with 54 non-ruptive CNs undergoing PCI were prospectively enrolled in the study. Baseline and procedural characteristics are summarized in Table 1. The mean age of the study population was 69.9 ± 9.0 years, with 85.7% of patients being male and 33.3% having diabetes mellitus. The mean left ventricular ejection fraction (EF) of the cohort was $43.3 \pm 13.2\%$ with one-third of patients exhibiting severe left ventricular dysfunction ($EF < 30\%$). Acute coronary syndrome was the presenting manifestation in 71.4% of the patients. Fourteen (66.7%) patients presented with triple vessel disease. The left anterior descending artery was the most frequently intervened.

The OCT assessment before and after IVL, as well as post-stent implantation, is detailed in Table 2. Before IVL, OCT revealed a mean calcium score of 3.7 ± 0.5 and a mean MLA at CN of $3.9 \pm 2.1 \text{ mm}^2$. The majority (66.7%) of patients exhibited a calcium arc of $>180^\circ$ at the site of CNs. Balloon dilation preceding IVL was required in 57.1% of the cases. The IVL device successfully traversed calcified lesions in all cases (100% success rate). Following IVL, OCT revealed calcium fractures in 40 out of 54 (74.1%) CNs with an average of 1.05 ± 0.72 fractures per CN. Fractures were predominantly observed at the base of the CN (80% of the CNs with fractures), while the remaining fractures occurred at the apex of the CN. Four CNs exhibited fractures at both the apex and base. Post IVL, the mean MLA at CN increased to $4.9 \pm 2.3 \text{ mm}^2$ with a mean MLA gain of $1.02 \pm 1.2 \text{ mm}^2$. After PCI, the mean MSA at the CN was $7.9 \pm 2.5 \text{ mm}^2$. Among patients with and without fractures, there was no statistically significant difference in the pre-IVL MLA, post-IVL MLA, post-PCI MSA, and MLA gain after stent placement at CN (Table 3). Optimal stent expansion ($>80\%$) at the CN was achieved in 85.7% of patients. Following IVL, none of the patients experienced perforation, slow flow, or abrupt vessel closure. Three (14.3%) patients exhibited

TABLE 1 Baseline and procedural characteristics.

| Baseline characteristics | N = 21 |
|--|--------------|
| Age (years) | 69.9 ± 9.0 |
| Male | 18 (85.7%) |
| Hypertension | 9 (42.9%) |
| Diabetes | 7 (33.3%) |
| Post CABG | 3 (14.3%) |
| CKD | 2 (9.5%) |
| Mean LVEF (%) | 43.33 ± 13.2 |
| LVEF ≤ 30% | 7 (33.3%) |
| CVA | 2 (9.5%) |
| Clinical Presentation | |
| Acute Coronary Syndrome | 15 (71.4%) |
| Chronic Coronary Syndrome | 6 (29.6%) |
| Procedural characteristics | |
| Target Vessel | |
| LAD | 11 (52.4%) |
| LCX | 1 (4.8%) |
| RCA | 2 (9.5%) |
| LM-LAD | 3 (14.3%) |
| LM-LCX | 1 (4.8%) |
| LM-LAD/LCX (Bifurcation) | 3 (14.3%) |
| LM Intervention | 7 (33.3%) |
| IVL device crossing success | 21 (100%) |
| Mean IVL balloon diameter (mm), mean (SD) | 3.2 ± 0.3 |
| Pre-IVL dilatation | 12 (57.1%) |
| Pre-stent dilatation | 20 (95.2%) |
| Number of stents per patient, mean (SD) | 1.80 ± 0.60 |
| Stent length (mm), mean (SD) | 31.55 ± 6.10 |
| Stent diameter (mm), mean (SD) | 3.24 ± 0.34 |
| Post-stent dilatation | 17 (81%) |
| Rota-tripsy (Rotational Atherectomy + IVL) | 3 (14.3%) |
| Procedural complications | |
| Flow limiting dissections | 0 (0%) |
| Perforation | 0 (0%) |
| Slow Flow or No-Reflow | 0 (0%) |

Abbreviations: ACS, Acute coronary syndrome; CABG, Coronary artery bypass graft; CKD, Chronic kidney disease; CSA, chronic stable angina; CVA, cerebrovascular accident; IVL, Intra vascular lithotripsy; LAD, Left anterior descending artery; LCX, Left circumflex artery; LM, left main artery; LVEF, left ventricular ejection fraction; PCI, Percutaneous coronary intervention; RCA, Right coronary artery.

TABLE 2 Optical coherence tomography features before and after intravascular lithotripsy (IVL).

| PRE - IVL OCT | (N = 21) |
|---|----------------------------|
| Calcium arc (in degrees) | 216.2 ± 81.4 |
| Calcium arc > 180° | 14 (66.7%) |
| The mean depth of the calcium (mm) | 1.03 ± 0.3 |
| The mean length of the calcium (mm) | 24.9 ± 10.6 |
| Total number of CNs | 54 |
| Pre-IVL CN height (mm) (N = 54) | 1.1 ± 0.3 |
| Arc of calcium in relation to CN | 360° 5 (23.8%) |
| | ≥180° to <360° 9 (42.9%) |
| | <180° 7 (33.3%) |
| Calcium score | 3.7 ± 0.5 |
| MLA at CN (mm ²) (N = 54) | 3.9 ± 2.1 |
| Proximal reference diameter (mm) | 3.7 ± 0.7 |
| Distal reference diameter (mm) | 2.9 ± 0.4 |
| POST - IVL OCT (N = 21) | |
| Calcium fracture/CN (N = 54) | 40/54 (74.1%) |
| Site of fracture at CN | Base 32 (80%) |
| | Apex 8 (20%) |
| | Both Base and Apex 4 (10%) |
| Number of fracture(s) (N = 54) | |
| No fractures | 14 |
| One fracture at the base of CN | 19 |
| Two fractures at the base of CN | 13 |
| One fracture at the apex of CN | 08 |
| Fractures at both the base & apex | 04 |
| Mean fracture number per CN (N = 54) | 1.0 ± 0.7 |
| Post-IVL CN height (mm) (N = 54) | 0.8 ± 0.2 |
| MLA gain (mm ²) | 1.02 ± 1.2 |
| Post-IVL MLA (mm ²) (N = 54) | 4.9 ± 2.3 |
| POST - PCI OCT (N = 21) | |
| MSA (mm ²) | 5.7 ± 1.8 |
| Stent expansion (%) | 84.2 ± 8.6 |
| MSA at CN (mm ²) (N = 54) | 7.9 ± 2.5 |
| MSA gain at CN from pre-IVL (mm ²) (N = 54) | 4.1 ± 1.7 |
| Stent expansion at CN (%) (N = 54) | 100.6 ± 18.2 |
| Stent apposition | 20 (95.2%) |
| Edge dissection | 1 (4.8%) |

TABLE 2 (Continued)

| PRE - IVL OCT | (N = 21) |
|--------------------|-------------|
| Asymmetric Index | 0.14 ± 0.08 |
| Eccentricity Index | 0.85 ± 0.07 |

Note. All variables were calculated with $N = 21$ unless otherwise specified. Abbreviations: CA+, Calcium; DRD, distal reference diameter; IVL, Intra vascular lithotripsy; MLA, minimum lumen area; MSA, minimum stent area; OCT, Optical Coherence Tomography; PRD, proximal reference diameter.

TABLE 3 MLA, MSA, and MLA gain before and after IVL in patients with and without calcium fractures.

| | Patients without calcium fractures | Patients with calcium fractures | p value |
|--|------------------------------------|---------------------------------|---------|
| Pre IVL MLA (mm ²) | 3.0 ± 1.5 | 3.7 ± 1.3 | 0.312 |
| Post IVL MLA* (mm ²) | 4.5 ± 2.1 | 4.6 ± 1.4 | 0.889 |
| Post PCI MSA* (mm ²) | 6.8 ± 2.2 | 8.0 ± 2.1 | 0.225 |
| MLA gain at calcium nodule after stent placement | 3.77 ± 1.46 | 4.32 ± 1.88 | 0.506 |

Abbreviations: IVL, Intravascular lithotripsy; MLA, Minimal lumen area; MSA, Minimum stent area.

*Post IVL MLA and MSA were measured at the same point of calcium nodule where Pre IVL MLA was measured (calcium nodule with the least MLA in the treated vessel).

TABLE 4 Clinical events at 30 days and 1 year follow-up.

| Clinical Events | 30 Days | 1 Year |
|-------------------------------------|-----------|--------------|
| All Cause death | 0/21 (0%) | 3/21 (14.3%) |
| Cardiac Death | 0/21 (0%) | 2/21 (9.5%) |
| Target Vessel Myocardial infarction | 0/21 (0%) | 1/21 (4.3%) |
| Target lesion revascularization | 0/21 (0%) | 0/21 (0%) |
| Target vessel revascularization | 0/21 (0%) | 0/21 (0%) |

major dissections, none of which were flow-limiting. All patients remained free from MACE during hospitalization and at the 30-day follow-up. At 1-year follow-up, all-cause death had occurred in three (14.3%) patients. Of these two [9.5%] were adjudicated as cardiac deaths—one patient had target vessel myocardial infarction leading to death due to definite stent thrombosis 2 months after the intervention, and one patient had sudden cardiac death at home at 12 months follow-up. One (4.8%) noncardiac death occurred due to terminal illness from cancer. (Table 4).

4 | DISCUSSION

The main findings of our study can be summarized as follows: (a) the use of coronary IVL for the modification of non-eruptive CN is safe; (b) IVL proved highly effective in the modification of non-eruptive CN; (c) IVL therapy resulted in the fracture of the majority of the CNs, with fractures most commonly occurring at the base, contributing to an increase in post-IVL MLA and final MSAs (Figures 1, 2).

The presence of calcified coronaries presents a significant challenge in stent delivery. Calcium nodules can cause disruption of drug-carrying polymer of the drug-eluting stent (DES) and contribute to under expansion of stents. Under expanded stents are associated with poor short and long-term outcomes in the form of stent thrombosis and in-stent restenosis.^{17–20} Preventing calcium-related under expansion of stent is more manageable than addressing it post-stent implantation. While severe calcification, particularly in the form of concentric calcium, serves as a predictor of under expanded stents, contemporary plaque modifying techniques like modified balloons, atherectomy devices, and lithotripsy have demonstrated effectiveness in adequately modifying calcium. These interventions contribute to achieving optimal stent expansion, even in these extensively calcified lesion subsets.²¹ Modifying lesions containing non-eruptive CNs with these devices presents a distinct challenge due to their eccentricity.

CN is a protruding eccentric mass of calcium with an underlying severe calcified plate. The incidence of CN increases with increasing severity of calcium in the artery and can be as high as 43.5%–48.5% in heavily calcified lesions.^{2,3} In our study, the majority of the CNs (67.7%) were present in lesions with more than 180° arc of calcium, signifying its association with heavily calcified vessels. The presence of CN in severely calcified lesions is an independent predictor of acute stent under-expansion and poor prognosis.⁴ Morofuji et al.³ reported that about half of the heavily calcified lesions requiring rotational atherectomy had CNs and their presence was associated with worse 5-year adverse events compared with calcified lesions without CNs. Similarly, Pengchata P et al.² showed that the presence of CNs significantly increases the occurrence of MACE within 5 years after PCI compared to non-CN patients where calcium modification was done by rotablation.

There are limited options available for the modification of non-eruptive CNs. Rotational atherectomy seems to be a viable option for CN modifications but may suffer a wire bias. Orbital atherectomy (OA) is an effective tool for CN modification with limited evidence.^{6,7} Pooled analysis of the CAD Disrupt trials has recently favored IVL for CN modification.¹²

In terms of safety outcomes, IVL demonstrates a minimal risk of peri-procedural complications.^{8–11} This was corroborated in our study, where no instances of flow-limiting dissections, no-flow, or perforations were observed, aligning with the findings from Ziad Ali et al.'s pooled analysis¹² comparing IVL in lesions with and without CNs.

Regarding safety outcomes, the absence of a direct comparison between RA and IVL in the context of non-eruptive CNs makes it

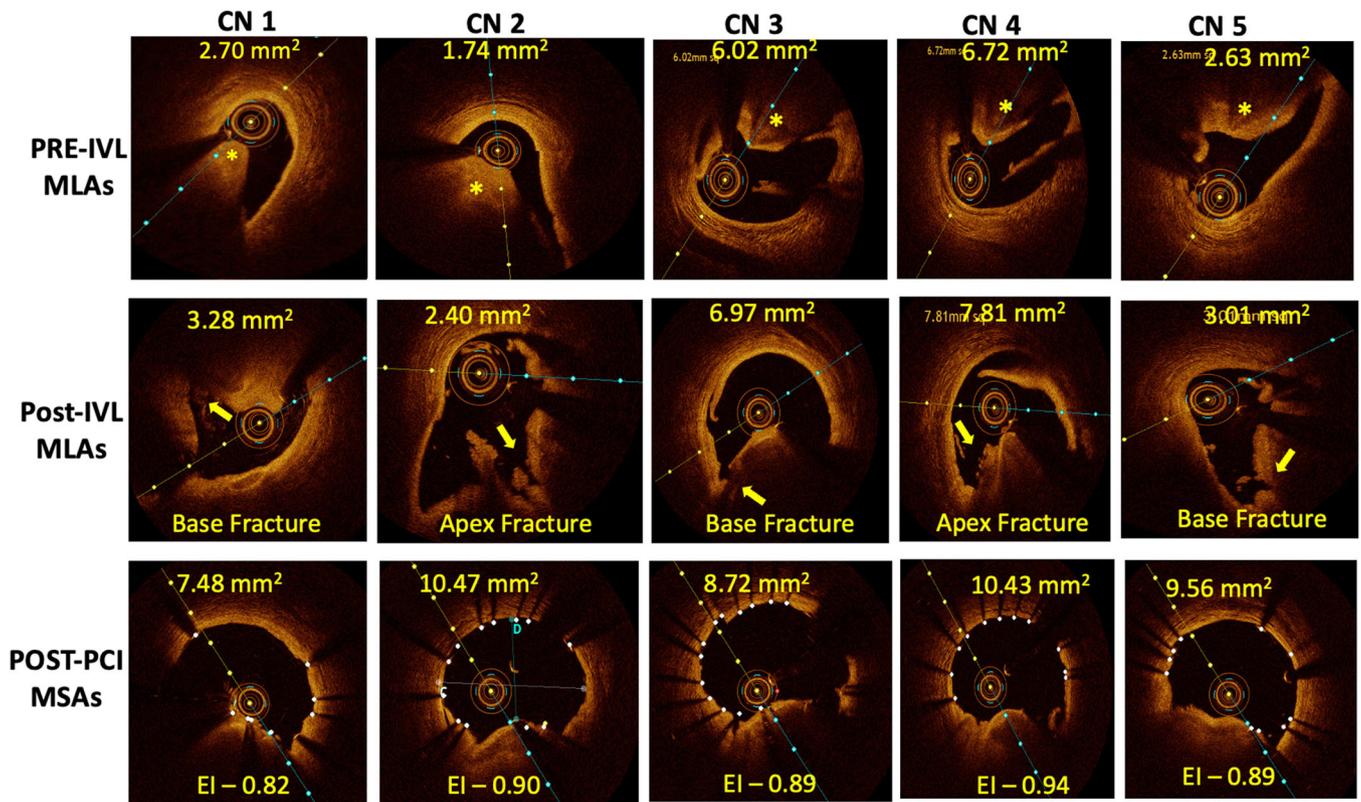


FIGURE 1 Optical coherence tomography (OCT) insight of intravascular lithotripsy impact on non-eruptive calcified nodule (CN). The upper row shows OCT images of five non-eruptive CNs (asterixis) with pre-IVL minimum lumen areas (MLAs). Middle row showing post-IVL MLAs and site of CN fracture (arrow). Lower row showing final minimum stent areas (MSAs) at CN with eccentricity index (EI). [Color figure can be viewed at wileyonlinelibrary.com]

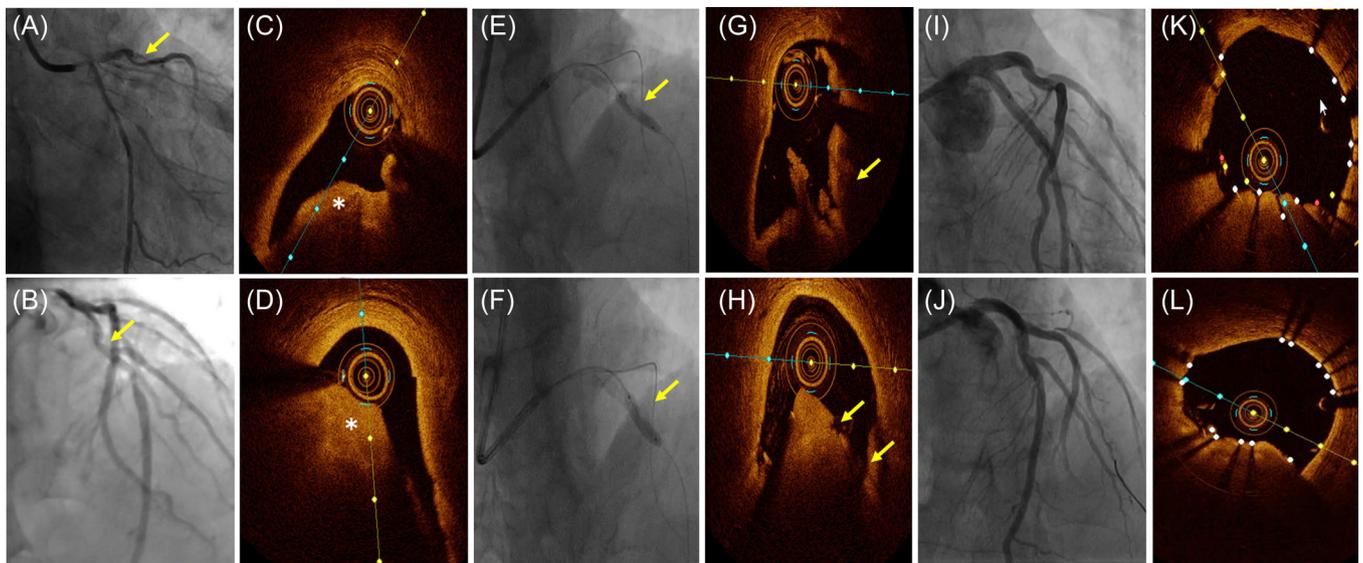


FIGURE 2 An illustrative case showing the impact of intravascular lithotripsy (IVL) on calcified nodule (CN). A 74-year-old male was admitted with non-ST elevation myocardial infarction. Coronary angiography (panel A, B) showed heavily calcified critical left main (LM) bifurcation disease with evident CN in the mid left anterior descending (LAD) coronary artery (arrow). Optical coherence tomography (OCT) revealed CN (Asterix) in mid-LAD and distal LM (panels C, and D). These nodules were modified with IVL sized to target artery and angiography showed a pre-therapy waist in the IVL balloon (panel E arrow) suggestive of the presence of CN and this waist in IVL balloon reduced markedly after 4 cycles of IVL therapy (panel F arrow). Post-IVL OCT showed fractures in CN at the apex (panel G arrow) and base (panel H arrow). The patient underwent LM bifurcation angioplasty with a modified double kissing crush technique with good angiographic (panel I, J) and OCT results (panels K, L). [Color figure can be viewed at wileyonlinelibrary.com]

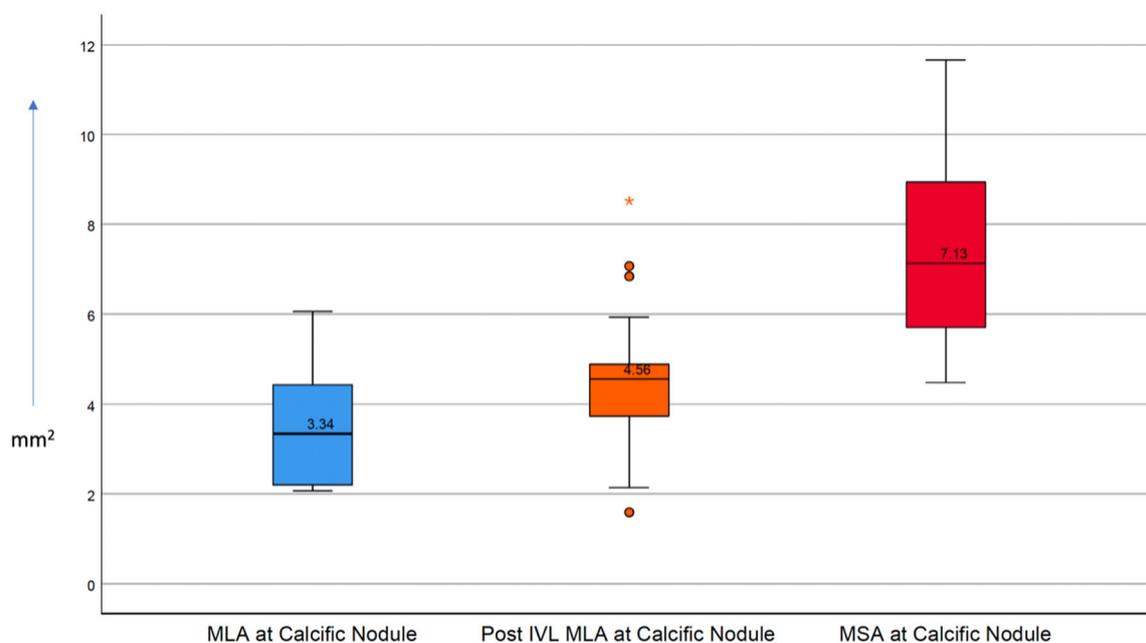


FIGURE 3 Box-plot depicting the sequential increase in areas at the calcified nodules after the use of intravascular lithotripsy and stent implantation. (MLA, minimum lumen area; MSA, minimum stent area). [Color figure can be viewed at wileyonlinelibrary.com]

challenging to ascertain any differences. However, both Pengchata et al. and Morojoji et al. demonstrated similar complications in all patients treated with RA, regardless of the presence of CNs. This implies that the risk of peri-procedural complications associated with RA in CNs is similar to that observed with RA in general. The incidence of peri-procedural complications while treating CNs with RA were enlisted as dissection and slow flow occurring at a rate of 2.3% in the study published by Pengchata et al.² Morijufi et al. showed dissection rates of 1.3% and no-reflow in 0.8% of CNs treated with RA.

Greater absolute stent expansion has consistently been linked to improved long-term stent outcomes with minimum stent area (MSA) serving as an independent predictor of subsequent MACE.²² Relative stent expansion of >80% has also been advocated by the European Association of Percutaneous Coronary Intervention for achieving good long-term outcomes.²³

In our study, IVL use was associated with a mean MLA at the site of CN of $4.9 \pm 2.3 \text{ mm}^2$, representing an increase from a pre-intervention MLA of $3.9 \pm 2.1 \text{ mm}^2$ (Figure 3). Additionally, we observed a minimum stent area at the site of the CN of $7.9 \pm 2.5 \text{ mm}^2$, with acceptable stent expansion in 85.7% of lesions. While previous studies exploring calcified nodules did not specifically assess vessel and stent areas at the site of the CN, Ziad Ali et al. noted in their pooled analysis that the site of maximum calcium on pre-intervention OCT was never the site of the final minimal stent area. Similarly, our study found that the MLA at the CN resulted in significantly larger stent areas (mean increase from 3.9 to 7.9 mm^2) compared to the final MSA ($5.7 \pm 1.8 \text{ mm}^2$), indicating adequate lesion preparation with IVL.

Ziad Ali et al.¹² also observed a stent expansion of 104.9% [78.5%–116.0%] at the site of maximum calcification in the CN group, which aligns closely with the stent expansion observed in our study at the site of the CN ($100.6 \pm 18.2\%$).

The key mechanism underlying stent expansion in severely calcified lesions is calcium fractures.^{13,24} These fractures increase vessel compliance, promoting increased stent expansion. In our study, 74.1% of the CNs exhibited demonstrable fractures on OCT, resulting in a mean MSA of $7.9 \pm 2.5 \text{ mm}^2$. In a pooled analysis of CAD disrupt trials,¹² IVL led to fractures in 78% of CN lesions, comparable to our findings. We also found that the base of the CN is the most common site of fractures present in 80% of CNs with fractures, while the remaining 20% exhibited fractures near the apex of the CN (Figure 1). To the best of our knowledge, this imaging feature has not been previously documented.

Other variables that could be utilized to assess the success of calcium modification in CNs and heavily calcified vessels are the asymmetric index and the eccentricity index. Suwannasom et al.²⁵ found device asymmetry and eccentricity to be an independent factor associated with adverse device-oriented composite outcomes. However, it's important to note that other studies have not consistently linked these indices with clinically driven TLR or stent thrombosis. Asymmetry in stent expansion is usually due to incomplete modification of the nodule. In a comparative analysis by Pengchata et al.,² although the prevalence of $\text{MSA} \leq 5.5 \text{ mm}^2$ and stent expansion were not significantly different between the CN and non-CN groups, TVR was significantly higher in the CN group. Furthermore, they observed a greater number of asymmetrical stent expansions in the CN group compared to the non-CN group. In their study, Pengchata et al. utilized deformability as a study variable, which included the asymmetrical

index, eccentricity index, and visual change in CN. They found that 77% of all CNs were deformable. While our study did not specifically investigate deformability as a composite index, we did observe an EI of 0.85 ± 0.07 and an AI of 0.14 ± 0.08 indicating symmetric expansion of the stent. Although the long-term outcomes of these variables remain unclear, their presence suggests optimization of CNs. We hypothesize that vessel symmetry and concentricity result in laminar flow, and hence better flow dynamics, thus theoretically decreasing the chances of restenosis.

While this was a single-arm study focusing on the application of IVL in calcified nodules, our research successfully showcased its safety, efficacy, and utility within this specific subset of patients.

5 | LIMITATIONS

Our study has several limitations, (1) The relatively small sample size utilized in this study may diminish the generalizability of the findings. However, there is a scarcity of research dedicated solely to investigating non-eruptive calcific nodules. Further studies with larger and more diverse cohorts are warranted to corroborate and extrapolate the observed trends. (2) While central Core Lab analysis for OCT and angiographic data was not conducted in this study, it is pertinent to highlight that the interpretation of these images involved the expertise of experienced interventional cardiologists. (3) This study being single-center and prospective, may potentially limit the broader applicability of the findings. Therefore, caution should be exercised in generalizing these findings to broader populations. Multi-center studies encompassing diverse patient demographics and clinical settings are warranted.

6 | CONCLUSION

In our single centre prospective study, we demonstrate the safety, efficacy, and utility of the IVL in the subset of patients with non-eruptive calcified nodules. We observed no major procedural complications, excellent lesion modification, and favorable 30-day and 1-year outcomes. However, long-term follow-up is necessary to assess the impact of IVL on restenosis rates in calcified nodules. With an increasing body of literature supporting the use of IVL in heavily calcified lesions, we believe that this paper contributes valuable insights into the management of patients with calcified nodules, a challenging aspect of interventional cardiology.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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