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INTRAVASCULAR LITHOTRIPSY: THERAPEUTIC AND DIAGNOSTIC APPLICATIONS IN HYPERTENSIVE PATIENTS WITH CORONARY CALCIFIED LESIONS

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ABSTRACT: Background: Intravascular lithotripsy (IVL) is an innovative method for treating heavily calcified coronary and peripheral lesions. It employs acoustic shock waves to create microfractures in calcified plaques, facilitating stent placement and improving vessel compliance. **Objective:** To assess the efficacy, safety, and potential applications of IVL in hypertensive patients with calcified coronary lesions, while exploring its diagnostic and therapeutic capabilities. **Methods:** A thorough review of the latest advancements and studies on IVL, with a focus on its use in hypertensive patients. Key studies, including the Disrupt CAD series, were analyzed for procedural success, safety, and clinical outcomes. The integration of IVL with imaging techniques such as intravascular ultrasound (IVUS) was also investigated. **Results:** IVL has shown high procedural success rates and minimal complications in treating calcified coronary and peripheral lesions. Studies have reported significant luminal gain post-IVL, with minimal residual stenosis. The Disrupt CAD studies confirmed the safety and efficacy of IVL, with minimal adverse events and substantial calcium fracture in treated lesions. IVL's effectiveness in managing specific clinically significant lesions, such as left main and nodular calcium lesions, was also demonstrated. **Conclusion:** IVL is a promising technology for modifying severely calcified coronary lesions, particularly in hypertensive patients. It enhances stent expansion and reduces complications associated with traditional atherectomy. The combination of IVL with advanced imaging techniques provides a personalized approach to treating calcified vascular diseases, improving patient outcomes and expanding therapeutic options.

INTRODUCTION: Lithotripsy widely used in the medical field by interventional cardiologists to treat patients with calcified plagues in coronary and peripheral vessels by creating a sonic pressure at almost 50atm (may vary depending on the severity or need) and delivering it inside the vessels which makes it to interact with the calcified plagues located within the vessels so as to create microfractures within the calcified plagues and paves way for effective stent placement.

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It is important for the interventional cardiologist and the health care team to prioritize the objectives in patients undergoing this procedure [1]. It aims to identify the lesions, to review the shockwave lithotripsy procedure and to thoroughly examine the risk factors associated with this procedure to provide a effective compliance statistics and health care development [2].

The concept of shockwave lithotripsy was deployed by urologists for the treatment of ureteral and renal calculi in which they used high energy acoustic pressure sonic waves to create microfractures in deep and superficial deposits of calcium to break them and to aid the deployment of a vascular stent. To determine the treatment modality imaging studies like intravascular ultrasound or optical coherence tomography is required to assess and define the density of the calcium deposit and to deploy the appropriate and optimal lesion modifying approach like atherectomy or Intravascular Lithotripsy (IVL) [3]. Percutaneous intervention that is conventionally used has increased in prevalence with respect to increased risk factors like diabetes, old age and hypertension. The need for percutaneous intervention in calcified coronary lesions has increased but has proven to be sub optimal outcomes by altering the drug kinetics and henceforth affecting the optimal stent expansion which in turn associates with poor clinical outcomes. Other common technologies like orbital and rotational atherectomy has posed its own limitations and complications and has failed to demonstrate optimal clinical efficacy which has made it necessary for the development of a new optimal, safe and an efficient treatment technique [4].

The dysfunction of vascular smooth muscles primarily contributes to the deposition of calcium in the blood vessels. This cascade occurs through micro vesicle and dysregulation of mineralization inhibitors leading to deposition of calcium within the medial and intimal layers if the vessel wall. Although there are reports of intracellular calcium deposition the precise significance of the pathophysiology has still remain uncertain. Calcifications range from a spectrum of moderate to severe which is present in one thirds of the patients presenting with acute coronary syndromes and up to fifty percentage of revascularisation procedures in peripheral arteries. Worse procedural success rates and occurrence of adverse effects like stent thrombosis and long-term rates of in stent restenosis and lesion revascularisation has led to the advent of lithotripsy for treatment of severely calcified lesions in the coronary and peripheral vasculature [5].

IVL has shown promising results in the management of calcified lesions in hypertensive patients with coronary artery disease and peripheral arterial disease. Studies have highlighted IVL as a safe and effective modality for treating heavily calcified arteries, leading to optimal stent expansion and low rates of complications [6, 7, 8, 9]. IVL has demonstrated high procedural success rates, with minimal residual stenosis and significant improvements in luminal cross-sectional area post-treatment. Additionally, IVL has been utilized in cases where severe calcifications influenced revascularization strategies, such as in patients undergoing transcutaneous aortic valve replacement (TAVR) [10]. The use of IVL in hypertensive patients has been associated with favourable outcomes, making it a valuable tool in the management of calcified lesions in both coronary and peripheral arterial diseases. In this review, we aim to analyse and understand the recent advancements in lithotripsy as an intervention for cardiac complications in hypertensive patients.

Scientific Overview: The system involves three hardware components namely the generator, a connector and a C2 catheter. The IVL balloon catheter system are sequenced into a array of semi compliant balloon filles with a mixture of saline and contrast. The system generates shock waves of low energy characterized by a short duration of ~5mcs, with a positive pressure peak and negative pressure trough components. The contrast filled balloon is inflated and opposed to the vessel wall, thereby providing interaction of fluid-tissue. The electric sparks creates vapour bubbles in the surrounding fluid medium in the integrated balloon. Expansion of vapour bubbles produces acoustic impulse which radiates circumferentially and transmurally through the layers of vessel in an unfocused manner. The acoustic impulses thus created interacts with high density calcified plagues without affecting the soft tissues, they disrupt the calcium by creating micro or macro fragments and thus increasing the compliance of the vessel [5].

Effect of IVL on Cardiac Rhythm: Acoustic shockwave impulses activated the mechano-sensitive cardiac ion channels which in turn induces localized myocardial depolarization, ventricular or atrial extrasystoles or ectopic beats can be a potential threat in inducing asynchronous cardiac pacing thereby imposing a potential threat of tachyarrhythmias, but it is only a theoretical risk only when the capture occurs during the vulnerable phase of repolarization, so far no cases of ventricular tachyarrhythmias induced by IVL has been reported.

Contraindications: It includes both the manufacturer cautioning to the medical professional handling the device and caution to not attempt this procedure in patients suffering from coronary in stent restenosis, manufacturer cautioning or recommendation states that the clinical should not attempt to deploy the device if they are not able to advance a 0.014 inch guide wire across the plague.

Therapeutic and Diagnostic Application of IVL in Hypertensive Patients: An interventional cardiologist is capable to perform the procedure without any further sub specialized need for training. The diameter of the catheter should be selected at 1:1 ratio relative to the targeted vessel and it should be inflated at a sub nominal pressure of 4atm, ten rounds of pulsatile acoustic waves are delivered with each emission cycle from the transmitters, subsequently the balloon is deflated then the procedure is repeated for two intervention cycles per 12mm target fields [11]. Adequate and proper apposition of the catheter and vessel wall is necessary for an adequate fluid-tissue interface to optimise efficient acoustic energy transfer. as mentioned above, the estimated peak pressure of the wave is 50 atm. It is the waves that generate the circumferential force by inflating the balloon, this has several advantages which includes reducing the risk of barotrauma, post dilation, vascular dissection and perforation after IVL for residual stenosis before stenting is often not required. The peripheral IVL catheter is used vividly in western countries for treatment of various peripheral vascular beds including popliteal, infra-popliteal, mesenteric, iliac and femoral, celiac and renal arteries [12].

IVL is a promising technology primarily used to modify severely calcified coronary vascular lesions before stent implantation [13]. IVL utilizes acoustic shock waves to induce circumferential and longitudinal calcium fracture, enhancing vessel compliance and facilitating stent expansion without high-pressure balloon dilation. While IVL is mainly applied in coronary artery disease, its therapeutic and diagnostic potential in hypertensive patients can be explored. By integrating IVL with imaging modalities like intravascular ultrasound (IVUS), AI-based systems, and microRNA expression analysis, a comprehensive approach can be developed for diagnosing and treating hypertension. This integration could provide a more personalized and effective treatment strategy for hypertensive patients by combining the benefits of IVL with advanced diagnostic tools and therapeutic interventions [14, 15, 16]. The schematic diagram of the above is represented in **Fig. 1.**

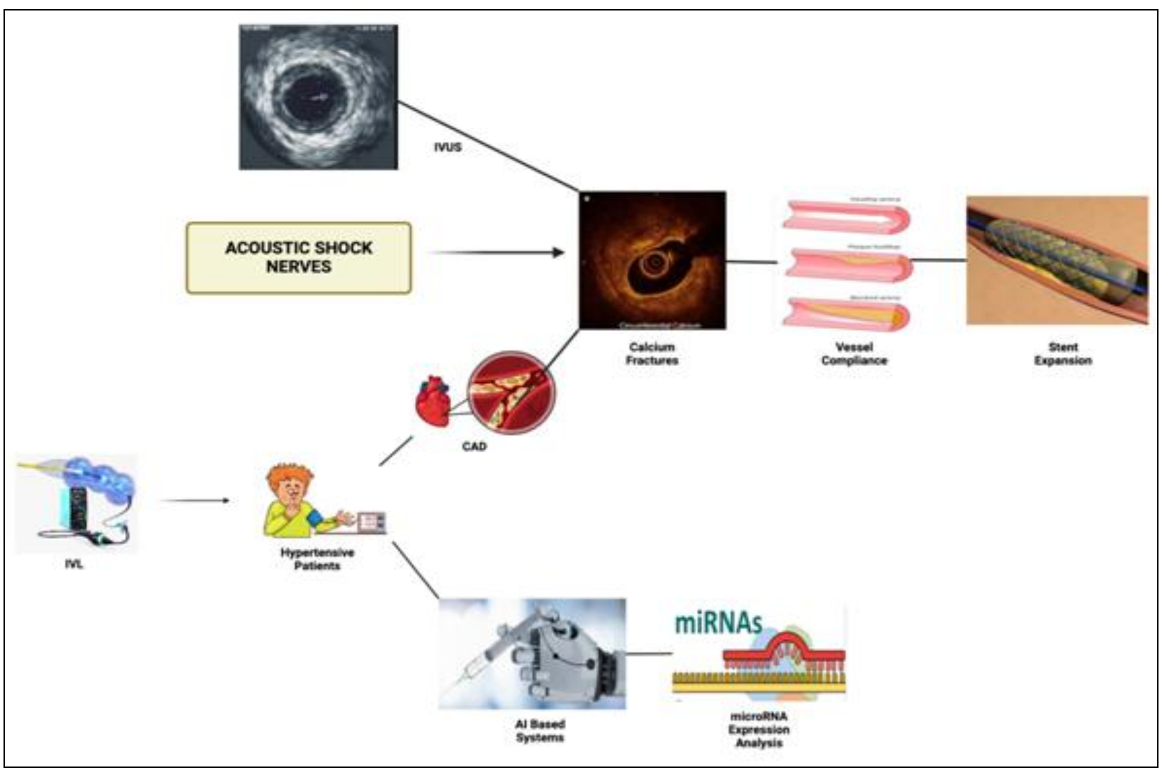

FIG. 1: INTEGRATION OF INTRAVASCULAR LITHOTRIPSY (IVL) IN THE DIAGNOSIS AND TREATMENT OF CORONARY ARTERY DISEASE AND HYPERTENSION

Safety and Effectiveness of Coronary IVL for treatment of Calcified Coronary Stenosis: The Disrupt CAD 1 study (Disrupt coronary artery disease study) was done in order to assess the extent of effectiveness and safety of IVL for these lesions. The disrupt cad study was a prospective multicentre, post approval study conducted at 15 hospitals in 9 countries. Patients with severe coronary artery calcification with a clinical indication for revascularization underwent vessel preparation for stent implantation with IVL. An optical coherence tomography sub study was done to assess the IVL effectiveness and its adverse effects and the characteristics of the fractures of the calcified plague [17].

Results of the study suggest that between a span of 11 months year 2018-2019, 120 patients were enrolled. Severe coronary artery calcification was present in 94.2 percent of lesions. Successful indication and use of IVL catheter was achieved in all patients. Post indication IVL angiographic acute luminal gain was 0.83 +/- 0.47mm, residual stenosis was 32.7 +/- 10.4 percent and which was reduced to 7.8 +/- 7.1 percentage post drug eluting stent implantation. Primary end point such as cardiac death, myocardial infarction occurred in about 5.8 percentage of the patients, which consists of 7 non q wave myocardial infarctions. There were no perforations, slow or no reflow. As far as the calcium fracture assessment is concerned in 47 patients with post percutaneous coronary intervention optical coherence tomography it was identified in 78.7 percentage of the lesions. The study reflects upon the successful indication of IVL catheter in severely calcified coronary artery lesions with minimal complications and high procedural success with substation fracture of the calcified lesions [18].

Specific Clinically Significant Lesions: Other important studies includes the feasibility and safety of IVL in left main (LM) lesions are supported and studied by a retrospective study analysis of 31 lesions treated by IVL. In this Study the minimal target stent area was achieved in 97.3 percentage of stented segments with no major adverse cardiovascular events [19]. And similar results were produced in a prospective study analysis of a registry cohort of 23 patients. In which successful stent indication and attainment of 30 percentage in stent residual stenosis of the target lesions with the help of thrombolysis was achieved in MI flow grade 3 in almost all patients [20]. The appropriate dimension of the IVL catheter that was used in this study had a diameter of 3.7 +/- 0.3mm, and a median of eight cycles and eighty pulses were generated. In case of large left main lesions, a catheter of 4mm may be used to fracture the calcium plague followed by a 1:1 NC balloon catheter to create expansion of the fractures created by IVL and prepare for a larger stent. One of the main concerns using IVL in left main lesions is the need to deliver the required energy to the prolonged vessel occlusion which could lead to severe ischemia. So they distributed the energy by providing pulses in small group with shorter balloon inflations to minimise the risk. With the advent of this approach only 2 out of 23 patients experienced severe arterial hypotension during inflation [21].

Long and Multiple Lesions: IVL treatment should be applied ideally from the distal to proximally located lesions. In long lesions, the physician can start by advancing the catheter as distally as possible, delivering energy and continue to advance the catheter. If multiple lesions are present it is recommended to deliver 20 pulses for each lesion and subsequently assessing the optimal points for remaining points. For Full therapeutic coverage in the vessel a 2mm overlap vessel is recommended when delivering energy in consecutive treatment areas. Multiple wires within the catheter enable the optimal transmission of energy from the generator to the emitters [22].

Nodular Calcium Lesions: In order to modify the eccentric calcium more pulses may be required as the emitter is further away from the calcium root. 80 pulses have been applied and an NC balloon is used to inflate the site for stent expansion to help determine procedural efficacy and to assess the requirement of an additional IVL catheter is needed to ensure full balloon expansion [21].

IVL and Stent under Expansion: Stent under expansion is undesirable situation that arises in coronary intervention leading to in stent restenosis and stent thrombus formation leading to stent thrombosis, this mechanism was explained by optical coherence tomography [20].

Numerous clinical cases have been reported and documented that supports the efficacy of intravascular lithotripsy in the treatment of restenosis related to under expanded coronary stent. A cohort study was conducted that suggests that using IVL in a stent restenosis the selected cohort has a procedural success lower than for de novo lesions.

Other Calcified Plagues Modifying Technologies Versus Intravascular Lithotripsy: Induced calcium modifications are certainly different from the preexisting technologies, the acoustic burst of energy contributes to the efficiency and not balloon inflation, on the other hand NC balloon or modified balloons reduce the risk of barotrauma and hence it reduces the risk of causing aortic dissection. Preparation of calcified plague is crucial for percutaneous intervention success. Other technologies like atherectomy suffer from wire bias whereas procedures like intravascular lithotripsy is free from subsequent eccentric plague guttering. Also, there is reduced risk of thrombosis and vascular bed overload, embolization of debris. It adds on to intervening the deeper calcium than the superficial calcium which is mostly done by the debulking technologies, which may have a negative compliance on the vessel wall compliance [19].

Electrophysiological Disorders: IVL is sensitive in patients with implantable pacemakers and defibrillators, the asynchronous capture which is created could interact with the capturing capabilities such as atrial or ventricular captures in patients with bradycardia. It is only the mechanical energy that is in the form of sonic pressure that is created interacts with the vessel wall and in fact no electrical current ever dissipates across the vessel wall, the sonic wave thus produces a stretch associated myocardial response. If there is any hemodynamic instability noted it is advisable to interrupt the IVL therapy temporarily [22].

IVL induced ventricular capture was termed as shocktopics, a retrospective study analysis was conducted for incidence of shocktopics and asynchronous cardiac pacing in patients undergoing coronary intravascular lithotripsy [27]. In this retrospective analysis 77.8 percentage of patients underwent IVL induced ventricular capture which automatically monitors pacing thresholds at regular intervals, with respect to the threshold the device determines a target output based on the programmable safety, margins and programmable minimum amplitude with no resulting adverse clinical events. In disrupt CAD3 study the significance and the occurrence of shocktopics have been noted and evaluated IVL induced capture was noted during IVL in 41.1 percentage of the cases. IVL induced capture did not result in ventricular arrythmias during the IVL procedure or immediately following the IVL procedure in any patient and was not associated with any adverse events [17]. Ventricular fibrillation induced by a lithotripsy pulse on T during coronary intravascular lithotripsy was noted, in case of a 79-year-old lady attended for elective percutaneous coronary intervention on a severe calcific in stent restenosis in mid right coronary artery. The RCA-ISR was difficult to dilate even after applying high balloon pressures inflations therefore coronary intravascular shockwave lithotripsy was used to disrupt and create fractures on calcific lesions thereby facilitating optimal balloon expansion. In the fourth treatment cycle ventricular fibrillation was triggered by the first pulse generated by lithotripsy create a VE on the T wave on the cardiac cycle. Obvious myocardial ischemia was absent prior to ventricular fibrillation. Circulation was reestablished after 2 minutes of cardiopulmonary resuscitation with a cycle of one direct current cardioversion [21].

Enhancing Healthcare Outcomes: IVL is an important tool that can be used in preparation of lesions and guidance of optimal percutaneous coronary interventions in the cardiac catheterization laboratory. Endovascular imaging ang optical coherence tomography followed by other imaging modalities are significant in defining and assessing the depth, circumferential extent and the density of the calcified lesions within the vessel wall so as to provide optimal and effective IVL procedure with utmost success rate in indication with minimal adverse events and devising an appropriate assessment technique for having achieved an adequate endpoint and implementation of this technique vividly in response to the welfare of community. A statistical representation of the types of IVL used in current trends is depicted in **Fig. 2** [22].

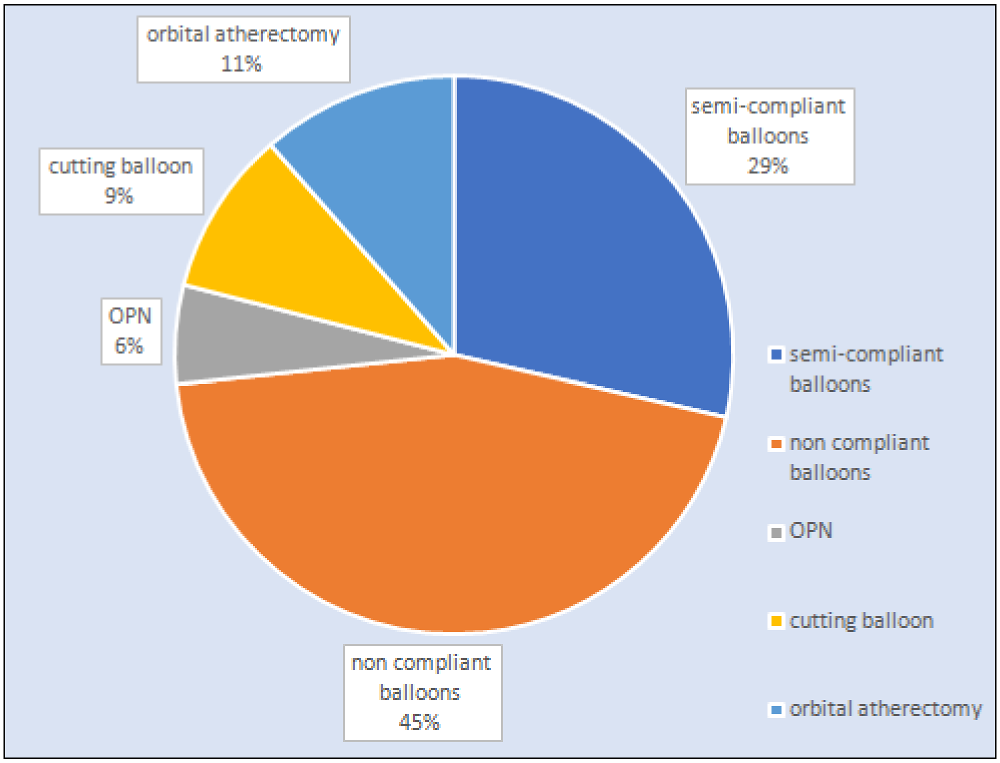

FIG. 2: STATISTICAL REPRESENTATION OF THE TYPES OF IVL USED

CONCLUSION: With the advent of novel technology, growing concepts, and published data on highly selected clinical scenarios and patients, retrospective and prospective studies are bridging gaps in scientific literature for various encountered and previously unobserved scenarios in disrupt CAD studies.

The integration of real-world data and expanding knowledge on techniques will enhance healthcare outcomes by ensuring optimal success rates with minimal clinically and instrumentally encountered adverse events. Further advancements in methodologies and the application of IVL to more complex and clinically challenging scenarios are expected to enhance this field. IVL is particularly impressive in the therapy of severe calcified coronary lesions, boasting a strong safety profile and a short learning curve. However, there remains room for improvement in the instrumental aspects of the catheter and in the appropriate preparation for various complex calcified lesions. Nevertheless, IVL has significantly impacted recent medical advancements, demonstrating considerable safety and success in treating calcified lesions in patients.

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