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In-Stent Restenosis: Achilles' Heel of Post-PCI Era

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Abstract

Despite advancements in stent design and polymer coatings over the past two decades, 1% to 2% of patients annually still experience in-stent restenosis (ISR). ISR reduces myocardial perfusion, may develop symptoms of myocardial ischemia, and thus leads to a high risk of myocardial infarction and cardiac death. Given that millions of drug-eluting stents (DES) are implanted globally every year, ISR remains a prevalent clinical issue with significant public health implications. Coronary intravascular imaging, includes intravascular ultrasound (IVUS) and optical coherence tomography (OCT), can help physicians gain deeper insights into the potential mechanisms of ISR. The preferred treatment strategy hinges on an accurate diagnosis and better understanding of etiology. The mechanism of ISR is multifaceted, and its treatment is challenging. Although the risk of ISR continues to decrease with advancements in DES application, further research is still needed to enrich the treatment options for ISR.

Keywords: In-stent restenosis, Drug-eluting stent, Intravascular ultrasound, Optical coherence tomography, Percutaneous coronary intervention

Commentary

In-stent restenosis (ISR) is a pathological condition discerned via digital subtraction angiography (DSA). It manifests as a luminal narrowing exceeding 50% within the stent or proximal to its termini by 5 mm, coupled with a diminution surpassing 20% of the initial vessel caliber after a successful percutaneous coronary intervention (PCI) [1]. Compared to bare-metal stents (BMS), the development of drug-eluting stents (DES) with anti-proliferative agents has led to a decrease in the incidence of ISR and target lesion revascularization (TLR). But the permanent presence of metal stents can result in risks such as inflammatory responses, neoatherosclerosis, and strut fractures [2]. The annual global augmentation in drug-eluting stents deployments has accentuated ISR's clinical significance, positioning it at the forefront of cardiovascular health concerns.

Epidemiology and Pathogenesis of ISR

The ubiquity of stent interventions has concomitantly escalated the prevalence of ISR episodes. Data from the last decade indicates that the incidence of ISR-PCI in the United States approximates 10% [3]. The clinical risk factors leading to ISR are complex. Extant literature delineates diabetes mellitus, smoking, older age, family history of coronary heart disease (CHD), history of restenosis, chronic kidney disease, and lipid metabolism disorders as salient contributors to ISR onset [4-6]. Furthermore, vascular lesion characteristics and surgical interventions can also increase the incidence of ISR [7,8].

The pathophysiological mechanisms governing ISR, albeit extensively studied, remain incompletely elucidated. Preliminary evidence underscores the centrality of inflammatory cascades and intimal hyperplasia in ISR's pathogenesis [9,10]. The Neutrophil-to-Lymphocyte Ratio (NLR), in contemporary studies, has been validated as an independent predictive factor for ISR [11]. Intimal hyperplasia is posited as the quintessential pathological substrate of ISR. In a seminal investigation, Songl et al. expounded on the synergistic interplay between intimal hyperplasia and suboptimal stent expansion in ISR genesis [12]. Advancements

in imaging modalities have engendered the conceptualization of "in-stent neo-atherosclerosis", offering novel insights into ISR's pathophysiological trajectory [13,14]. Such revelations are instrumental in shaping future therapeutic paradigms.

ISR: Imaging Insights into Pathogenesis and Therapeutic Implications

Traditional coronary angiography was unable to accurately evaluate lesion-specific plaque characteristics and stent implantation outcomes, rendering it inadequate for the comprehensive diagnosis and management of ISR [15]. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) offer superior resolution of plaque morphologies, thus enabling an in-depth investigation into the etiology of ISR and lesion assessment. IVUS has provided further insight into the understanding of vascular remodeling after stent implantation, the role of stent underexpansion, and the distribution of neointimal hyperplasia (NIH) in ISR. OCT has been shown to be superior to IVUS in the detection of malapposition of stent struts, stent edge-related dissections and stent fractures. Furthermore, utilizing the optical principles, it can penetrate calcified tissues, enabling the measurement of calcified plaque thickness, volume, and dimensions [16]. Both IVUS and OCT provide interventionists with guidance for adequate lesion pretreatment, includes selecting stents of appropriate length and size to achieve maximal stent area, minimizing geographical lesion miss, identifying incomplete stent apposition and stent underexpansion [17].

While the primary lesions of ISR have been well-characterized, contemporary imaging modalities have unveiled the phenomenon of "in-stent neo-atherosclerosis" as a pivotal determinant in ISR's pathogenesis [18]. The progressive elucidation of ISR's underlying mechanisms, bolstered by these imaging insights, would be helpful for the refinement of therapeutic strategies of ISR in the clinical community.

Contemporary Therapeutic Modalities for ISR

The therapeutic landscape for ISR, despite considerable advancements, lacks a universally endorsed optimal strategy. Historical clinical trial data underscore the efficacy of repeated DES implantation and Drug-Coated Balloons (DCB) dilation, both demonstrating commendable clinical outcomes [19,20]. In alignment with these findings, the 2018 ESC guidelines have promulgated the adoption of both aforementioned strategies for ISR treatment [21]. Furthermore, the guidelines extol the virtues of intracoronary imaging modalities, notably IVUS and OCT, for discerning ISR etiologies, lesion appraisal, and therapeutic guidance.

In leveraging IVUS/OCT for lesion evaluation, clinicians are urged to adopt an integrative tri-layered approach, encompassing:

Stent-related factors:

- Stent underexpansion
- Suboptimal stent size
- Stent fracture
- Stent type
- Stent gap or overlapping stents

In-stent factors:

- Neointimal hyperplasia
- In-stent neoatherosclerosis
- Calcification or embolization
- Homogeneity or heterogeneity tissue
- Focal or diffuse type
- Severity of obstruction

Extra-stent determinants:

- Multiple stent layers
- Vascular calcification
- Calcified lesions
- Vessel size
- Residual plaque burden

Such a meticulous evaluation paradigm facilitates a nuanced understanding of ISR, thereby tailoring the therapeutic approach to the individual patient's pathology.

Repeated DES implantation in ISR: Clinical Implications and Evidentiary Support

In the therapeutic milieu of ISR, repeated DES implantation has emerged as a cornerstone intervention [22]. The most recent American College of Cardiology (ACC)/American Heart Association (AHA) coronary revascularization guidelines recommend repeated DES for treatment of ISR-PCI (Class IA) [23]. Regardless of whether the initially implanted stent was a DES or a bare metal stent, repeat DES implantation consistently demonstrating superior clinical outcomes. For example, the DAEDALUS study, included a meta-analysis of 10 randomized clinical trials assessing the efficacy of paclitaxel-coated DCB vs. DES in treating ISR [24]. The primary endpoint was TLR, indicative of recurrent stenosis within the target lesion segment. Concurrently, the primary safety endpoint amalgamated outcomes such as all-cause mortality, myocardial infarction, and target lesion thrombosis. Following a longitudinal observation spanning 3 years,

the data elucidated that for DES-ISR cohorts, repeated DES implantation not only showcased an impeccable safety profile but also outperformed DCB in terms of efficacy.

DCB in ISR Management: Clinical Insights and Advancements

While the repeated DES implantation has garnered significant attention in the ISR therapeutic domain, the utilization of DCB is increasingly gaining traction in contemporary clinical practice. DCBs have outstanding therapeutic advantages with the addition of an anti-proliferative drug coating on the balloon. The design facilitates a uniform drug dissemination along the vascular endothelium, avoiding repeated stent implantation [25]. Moreover, the therapeutic intervention employing DCBs is amenable to repetition, enhancing its clinical versatility [26]. Presently, paclitaxel stands out as the predominant drug choice for DCB coatings [27].

Two critical issues need to be considered when to manage ISR: the type of stent implanted (BMS or DES) and the presence of mechanical issues preventing full stent expansion. The former can be overlooked in the era of DES, the latter should be best identified using intravascular imaging, which is recommended for all ISR cases. Subsequently, the surgeon can decide whether to choose DCB or DES for treatment. If multiple expansions yield suboptimal results (e.g., significant dissections or residual stenosis >40%), DES should be preferred. For DES-ISR, re-implantation of a DES has proven more effective than DCB, making it the first-line treatment in such scenarios. However, in certain situations, such as when two stent layers already exist, initiating treatment with a DCB might be more favorable [28].

Beyond the conventional ISR therapeutic modalities, in instances where ISR is concomitant with calcified lesions and suboptimal stent expansion, an integrative approach harnessing rotational atherectomy (colloquially termed "rotablation") in conjunction with IVUS technology is gaining clinical endorsement [29]. Nevertheless, during such intricate procedures, a meticulous understanding of the operational intricacies is paramount to safeguard patient well-being and achieve the desired therapeutic outcomes.

ISR: Implications for Cardiovascular Risk

The emergence of ISR is not merely a procedural complication but carries profound implications for subsequent cardiovascular events, including angina, acute myocardial infarction, and cardiac death [30]. Given these ramifications, delineating the risk landscape of ISR is of paramount clinical relevance.

A recent large cohort study published in Eurointervention analyzed the long-term clinical outcomes of ISR-PCI. The findings underscored that ISR lesions stand as independent risk factor for major adverse cardiac events (MACE) after PCI intervention. Notably, the propensity for major adverse cardiovascular and cerebrovascular events (MACCE), all-cause mortality, myocardial infarction, repeat revascularization, and TLR was significantly accentuated in the ISR-PCI cohort compared to those undergoing primary lesion PCI. An intriguing revelation from the study was the predilection of ISR lesions to manifest more as Acute Coronary Syndrome (ACS) in real-world clinical settings, challenging the conventional notion of ISR predominantly presenting as stable angina [31].

ISR: Current Insights and Future Directions

The evolution of medical interventions has ushered in notable progress in addressing ISR [21]. Yet, ISR persists as a formidable clinical conundrum. The underpinnings of ISR are multifaceted, with prevailing consensus attributing it to inflammatory processes and intimal hyperplasia [32]. Contemporary research endeavors have embarked on a granular exploration of ISR's histopathological dynamics, underscoring the imperative for sustained investigative efforts. Novel approaches to prevent or reduce the trigger factors of ISR are emerging. The EPC-capturing technology has been applied to a sirolimus-eluting stent, with a luminal surface covered with an anti-CD34+ antibody able to capture EPCs might promote a 'controlled' healing [33]. Prostaglandin E1 (PGE1), especially its nanoliposome dosage form, has been reported to exert a potential therapeutic effect on the reduction of ISR by inhibiting platelet aggregation, reducing the inflammatory response, improving microcirculation and acting on vascular endothelial cells to dilate blood vessels [34]. Theoretically, the application of nanoliposome alprostadil after PCI could early reduce the occurrence of ISR, but more clinical studies are needed to apply it to practice.

Presently, a unified therapeutic blueprint for ISR remains elusive. The 2018 ESC guidelines proffer dual primary modalities for ISR management, accentuating the adjunctive role of intracoronary imaging modalities such as IVUS/OCT [21]. With more accurate imaging and appropriate measures for different types of ISR, it can better guide the clinical diagnosis and treatment of ISR patients and improve the clinical prognosis.

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