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In-Stent Restenosis, the Achilles' Heel of Percutaneous Coronary Intervention: The Predictive Role of High-Sensitivity C-Reactive Protein

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Editorial:

Percutaneous coronary intervention, including intracoronary stenting represents a major revolutionary game-changer in the field of interventional cardiology. Intracoronary stents have been shown to increase procedural safety and reduce the number of cardiovascular events compared to balloon angioplasty. However, it remains fraught with the perils of in-stent restenosis [1].

In-stent restenosis (ISR) has always been the Achilles' heel of percutaneous coronary intervention (PCI). It is defined as the degree of lumen diameter reduction following PCI.

The etiology behind ISR is multifactorial and cannot be attributed to single mechanism. The occurrence of ISR ranges between 32 and 55% in the pre-stent era to 17–41% in the era of bare-metal stents to <10% with the second generation drug eluting stents and drug-coated balloons [2]. Prior to the stenting era, ISR was usually secondary to elastic recoil forces of the vessel including vascular remodeling. In the post stenting era, ISR is usually secondary to two mechanisms: neo-atherosclerosis or neointimal hyperplasia [3].

The former mechanism is related to incomplete endothelial regeneration leading to incomplete endothelial stent strut coverage. This, in turn, leads to an accelerated atherosclerotic process by stimulating excessive lipid uptake [4]. This is more commonly seen in drug-eluting stents.

The latter mechanism is a sequela of a chronic intimal wall stress induced by stent struts. This leads to vascular smooth muscle cell stimulation and migration to the tunica intima along with the activation of various inflammatory processes leading to neointimal hyperplasia [5]. This is more commonly observed in bare-metal stents [5].

In addition to a myriad of other clinical conditions, ISR is associated with increased mortality [6]. Clinically, ISR translates into recurrence of progressively worsening anginal symptoms, or an acute coronary syndrome. Therefore, the predictors of ISR have been an intense area of research aiming to decrease its incidence.

In general, the causes of ISR are either procedural, lesion related or patient related [2]. The former two causes comprise lesion length, ostial/bifurcation lesions, multi-vessel coronary artery disease, vessel size, stent length, stent under expansion and stent type. The main factors affecting the latter include the presence of diabetes, female sex, age, and genetic factors.

Lending credence to the aforementioned, coronary stenting-induced chronic inflammation lies at the core of ISR. The surge of systemic inflammatory biomarkers post-PCI and their predictive role in the occurrence of ISR has been a major research focus. Of those biomarkers emerges, high sensitivity C-reactive protein (hs-CRP). Historically, the role of hs-CRP is more defined in the primary prevention of cardiovascular disease, and it is considered a cardiovascular risk enhancing factor. According to the 2019 ACC/AHA guideline [7] on the primary prevention of cardiovascular disease, hs-CRP level of >2 mg/L is included in the computational estimation of the risk of atherosclerotic cardiovascular disease.

However, the role of elevated hs-CRP levels in the secondary management of coronary artery disease, namely in-stent restenosis is less defined. It is well known that hs-CRP is a hepatic acute phase reactant that is produced as a culmination of the chronic inflammatory cascade resulting from PCI-induced chronic vascular injury leading to the amplification of the inflammatory cascade [8].

The clinical impact of the predictive role of the post-PCI systemic inflammatory surge on the identification of ISR remains controversial with some data linking the degree of systemic inflammation to post-PCI adverse clinical outcomes [9,10], while others demonstrating that the levels of inflammatory markers, as CRP, are similar after PCI regardless of the presence of ISR [11,12]. In view of these aforementioned conflicting reports, more studies are needed to evaluate the association between systemic inflammatory markers and ISR after successful PCI while controlling for confounding variables.

In the current issue of Cardiovascular Revascularization Medicine, Baktashian et al. present an investigative analysis on the association of ISR with multiple patient characteristics including hs-CRP [13]. This was a case-control study of 104 patients with ISR, and 202 patients without ISR excluding patients with acute coronary syndromes.

Baseline characteristics as fasting blood glucose (FBG), total cholesterol, high density lipoprotein, hs-CRP, and serum triglycerides were collected. The authors found a significant association of ISR occurrence with the presence of diabetes (60% with ISR), stent type, duration and number (60.3% ISR in bare metal stents versus 39.7% in drug eluting stents), FBG, serum triglyceride level, and hs-CRP levels. In the sub-cohort of patients with diabetes and ISR, 46.9% had hs-CRP < 2.64 mg/dL, and 57.9% had hs-CRP levels of >2.64 mg/dL. However,

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there was no association between diabetes and hs-CRP levels. In a receiver operating characteristic curve (ROC) analysis, a cut-off hs-CRP level of 2.64 mg/dL was selected yielding a specificity of 59.36%, and sensitivity of 62.64%.

Admittedly, diabetes mellitus remains one of the most important independent predictors of ISR whereby it remains significantly associated with ISR in the sub-cohort of patients with hs-CRP <2.64 mg/dL. On the other hand, adjusting for the presence and duration of diabetes, hs-CRP remains significantly associated with ISR, and relates positively with obesity. Furthermore, the study shows that hs-CRP remains significantly associated with ISR after adjusting for stent type and for the time elapsed since stent implantation. In the sub-cohort of patients with ISR, and hs-CRP levels below 2.64 mg/dL, ISR was noted to occur earlier, and this is believed to be secondary to sub-optimal technical and procedural related factors as the underlying mechanism of ISR, while systemic procedure-independent factors were more prominent in the sub-cohort of patients with ISR and hs-CRP levels above 2.64 mg/dL.

This study fortifies the existing literature with more positive signals on the possible utility of hs-CRP levels in predicting ISR. That coupled with the presence of diabetes mellitus appear to have a robust impact on the identification of ISR. However, the limitations of the study include the absence of data concerning the presence of optimal procedural and technical characteristics including coronary vessel caliber, optimal intraprocedural stent expansion, and the indication of the index procedure during stent implantation.

In-stent restenosis remains a complex entity with an interplay of multiple etiologic factors including systemic inflammatory processes, and procedural-related factors. There remains a significant heterogeneity among the studies discussing ISR in relation to hs-CRP. The clinical applicability of the predictive nature of hs-CRP levels in the identification of ISR appears promising. Yet, in the absence of robust larger multi-center clinical trials, and cut-off hs-CRP levels with acceptable sensitivity and specificity thresholds for clinical utilization, the ability to extrapolate meaningful clinical data remains limited at the time being.

References

[1] Al Suwaidi J, Berger PB, Holmes Jr DR. Coronary artery stents. JAMA 2000;284(14):1828–36.

[2] Buccheri D, Piraino D, Andolina G, et al. Understanding and managing in-stent restenosis: a review of clinical data, from pathogenesis to treatment. J Thorac Dis 2016 Oct;8(10):E1150–62.

[3] Eeckhout E, Serruys PW, Wijns W, et al. editors. Percutaneous interventional cardiovascular medicine: the PCR - EAPCI textbook. Europa Ed. PCR Publ, 2012:785–826.

[4] Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333–42.

[5] Piek JJ, van der Wal AC, Meuwissen M, et al. Plaque inflammation in restenotic coronary lesions of patients with stable or unstable angina. J Am Coll Cardiol 2000;35:963–7.

[6] Cassese S, Byrne RA, Schulz S, et al. Prognostic role of restenosis in 10004 patients undergoing routine control angiography after coronary stenting. Eur Heart J 2015;36:94–9.

[7] Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol 2019;March 17:[Epub ahead of print].DOI: https://doi.org/10.1016/j.jacc.2019.03.010.

[8] Li JJ. Inflammatory response, drug-eluting stent and restenosis. Chin Med J (Engl) 2008;121(6):566–72.

[9] Gibson CM, Karmpaliotis D, Kosmidou I, Murphy SA, Kirtane AJ, Budiu D, et al. Comparison of effects of bare metal versus drug-eluting stent implantation on biomarker levels following percutaneous coronary intervention for non-ST-elevation acute coronary syndrome. Am J Cardiol 2006;97(10):1473–7.

[10] Li J-J, Ren Y, Chen K-J, Yeung AC, Xu B, Ruan X-M, et al. Impact of C-reactive protein on in-stent restenosis: a meta-analysis. Tex Heart Inst J 2010;37(1):49.

[11] Bhatt DL. Inflammation and restenosis: is there a link? Am Heart J 2004;147(6):945–7.

[12] Tan Z, Li L, Ma Y, Geng X. Prognostic values of high-sensitivity C-reactive protein for patients receiving percutaneous coronary intervention. Biomed Res 2017(4):28.

[13] Baktashian M, Soflaei S, Kosari N, et al. Association of high level of Hs-CRP with in-stent restenosis; a case-control study. Cardiovasc Revasc Med 2019;20(7):583–7.