Coronary restenosis: mechanisms, diagnosis and treatment in contemporary practice

Reestenose coronária: mecanismos, diagnóstico e tratamento na prática contemporânea

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ABSTRACT – In-stent restenosis stands out among the late complications of coronary angioplasty. Initially, it occurred in up to 60% of procedures using only balloons, but dropped to 10% with the advent of drug-eluting stents, even in more complex anatomic and technical scenarios. However, efforts have been made to achieve long-lasting results with no need for new revascularizations. Broad knowledge of pathophysiology, of predisposing risks factors for restenosis, and of new concepts, such as neoatherosclerosis, is paramount to its prevention. This article revises these aspects, as well as the importance of imaging methods and resources currently available for treating coronary restenosis.

Keywords: Coronary restenosis/diagnostic imaging; Angioplasty, balloon, coronary; Stents; Atherectomy, coronary

RESUMO – Dentre as complicações tardias da angioplastia coronária, destaca-se a reestenose intra-stent. Sua taxa, que inicialmente alcançava até 60% dos procedimentos efetivados apenas com balão, foi reduzida para patamares de até 10% com o advento dos stents farmacológicos, mesmo em cenários de maior complexidade anatômica e técnica. Entretanto, esforços vêm sendo envidados, na busca de resultados duradouros e livres da necessidade de novas revascularizações. O conhecimento aprofundado da fisiopatologia, dos fatores de risco predisponentes à ocorrência da reestenose e de novos conceitos como neoaterosclerose é fundamental para sua prevenção. Neste artigo, revisaremos tais aspectos, bem como a importância dos métodos de imagem e os recursos atualmente disponíveis para o tratamento da reestenose coronária.

Descritores: Reestenose coronária/diagnóstico por imagem; Angioplastia coronária com balão; Stents; Aterectomia coronária

GENERAL ASPECTS AND HISTORY

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) and its application to a growing number of patients, two main adverse events associated with the method have been identified: thrombosis and in-stent restenosis (ISR). The latter is the object of this review. Rates of ISR with balloon PTCA were high (40 to 60%), and the major mechanisms were acute and chronic elastic recoil, and negative constrictive remodeling of the vessel.1

With the introduction of bare-metal stents, the deleterious phenomenon of acute elastic recoil of the vessel was eliminated, but a new entity was introduced, i.e., neointimal hyperplasia (NIH), which has linear correlation with late luminal loss of the stent. As a consequence, ISR rates were reported as 20 to 35%, with clinical and angiographic variables as risk factors.2 Brachytherapy involves the concept of endovascular radiation, and was initially studied in this scenario. However, it resulted in edge loss and high rates of late in-stent thrombosis, being excluded for clinical application.3

The next step was key for reducing the incidence of ISR: the introduction of drug-eluting stents (DES). The first-generation of this group, sirolimus- (Cypher®) or paclitaxel-eluted (Taxus®), reduced ISR to very low levels, for both simple (close to 0%)
and complex lesions (10 to 15%). This fact significantly impacted on reduced number of new revascularizations. The evolution to new generations of DES brought favorable changes in terms of safety, by reducing the risk of in-stent thrombosis. However, it is still challenging to further reduce ISR rates with the current stents, since their use has been disseminated for more complex lesions, and late failure due to neoatherosclerosis has emerged as a new obstacle to be overcome.

DEFINITION AND CLASSIFICATION

In order to have a uniform nomenclature, the binary concept of restenosis is used; that is, reappearance of the lesion with ≥50% obstruction of the vessel lumen in the segment treated (inside the stent and at the edges, 5mm downstream and upstream). This concept was based on physiology studies, which demonstrated impairment of coronary flow reserve from this degree of vessel lumen obstruction.

A classification system was established in 1999 to differentiate ISR patterns. Two major patterns were described, with several subtypes: focal ISR and diffuse ISR (Figure 1). Usually, the ISR pattern in the bare-metal stents group is diffuse and may be of the diffuse proliferative subtype, when it involves the edges of the stent. In DES, the most commonly found pattern is focal ISR, with the proximal edge being the most common site of occurrence. However, about 20% of cases of ISR in DES present a diffuse pattern and, sometimes, an occlusive pattern.

RISK FACTORS FOR IN-STENT RESTENOSIS

Over time, it was possible to identify factors associated with higher incidence of ISR. We have, therefore, patient-related factors and the most important are diabetes mellitus, especially insulin-dependent, chronic renal failure under dialysis, and clinically unstable individuals. Angiographic factors also play a key role, such as lesions in thin vessels, long lesions (>20mm), tortuous segments, thrombus, ostial lesions, venous grafts (saphenous grafts), very calcified vessels, chronic occlusions, and bifurcations. Factors related to the procedure are also crucial, including the degree of post-procedural residual stenosis and, specifically in the case of stent deployment, poor expansion, which is easily identifiable by intracoronary imaging methods.

Among all these angiographic and clinical factors, diabetes is one of the most studied and most strongly involved, both for bare-metal stents and DES in-stent restenosis. Therefore, it is an important topic in decision-making when discussing the possibility of PTCA in a given patient with manifest coronary disease.

CLINICAL PRESENTATION

Historically, ISR has manifested with stable symptoms, with no direct impact on important unfavorable clinical outcomes. Patients have been classically described as presenting stable angina or silent ischemia, usually between 3 and 6 months after intervention, and with very satisfactory results after a new intervention. This was consonant with the predominant form of ISR, NIH, characterized by progressive, homogeneous proliferation of smooth muscle cells (Figure 2). Nonetheless, more
recent studies have also associated ISR with acute coronary syndrome in 30% to 50% of cases, and it may lead to acute myocardial infarction (MI), with artery occlusion in 5% of cases. The ISR pattern most related to this type of acute manifestation is neoatherosclerosis, which is the major cause of ISR in new generation DES. These cases can often be misinterpreted as in-stent thrombosis. The angiographic pattern, lesion behavior during balloon insufflation, and medical history of the patient may help differentiate between ISR and thrombosis. The use of intravascular imaging is paramount in such cases.

**PATHOPHYSIOLOGY OF IN-STEM RESTENOSIS**

**Mechanistic factors**

The correct understanding of the ISR mechanism is crucial to guide and optimize new interventions. Often there is a mechanical failure in stent deployment, and if properly recognized, it can be corrected in a new approach. Stent underexpansion is a pivotal factor to trigger ISR in both bare-metal and drug-eluting stents. It can be caused either by low insufflation pressures during stent deployment or stent undersizing. Another reason is inadequate expansion, even with good insufflation pressures and adequate sizing, when a highly calcified lesion is treated. In these cases, adequate preparation of the lesion prior to stent implantation, with suitable pre-dilation and use of rotational atherectomy may reduce this occurrence.

However, many patients present ISR even with appropriately expanded stents. Some possible findings may explain the occurrence of ISR: stent displacement, lack of full coverage of the treated lesion, gaps between stents and as more recently described, stent fracture (Table 1). The latter is an entity initially described in 2004, which presents a focal pattern, reflecting repeated trauma at this site, and occurring regardless of the type of DES used. Stent fracture is more frequently found in patients with long stents, overlapping stents, critical lesions vigorously dilated, myocardial bridge at the edge of the stent, and areas of significant curvature. The right coronary artery and the saphenous vein grafts are the most affected territories as a consequence of the intense mobility during systole, in addition to tortuosity and angulation.

**Biological factors**

Endothelial aggression is the main mechanism to explain the occurrence of ISR in bare-metal stent. However, with the advent of DES, other biological mechanisms have been involved, including resistance to antiproliferative drugs and hypersensitivity reactions to the stent polymer. Resistance to antiproliferative drugs was initially very well documented in the cancer setting, and later, in coronary intervention. Some drugs, such as sirolimus and paclitaxel, may present the so-called pharmacological resistance by genetic expression, characterized mainly by mutations in genes encoding proteins implied in the metabolism of these drugs.

Resistance to the metal platform is another important aspect to be considered, and was well studied and described in platforms that today are obsolete, such as gold and molybdenum. Resistance to the platforms used today, although it has been theorized and speculated, has not been proven so far. Polymer hypersensitivity is a well-studied and proven factor in the DES era. Drug-eluting stents have polymers for drug storage and release, which promoted delayed vessel hypersensitivity. Although the inflammatory reaction that occurs shortly after arterial injury from stent deployment is a critical factor for the neointimal response, the persistence of the inflammatory response after 90 days, caused mainly by non-biocompatible polymers of the first generation DES, is a factor strongly associated with ISR and very late thrombosis in these devices.

**Neoatherosclerosis**

Neoatherosclerosis is defined as the presence of atherosclerotic disease within the neointima in a segment treated with stent. The pattern found can range from abnormal intimal thickening with presence of intercellular lipid accumulation, to a ruptured thin-layer fibroatheroma, which usually presents with acute coronary syndrome (Figure 3). The incidence of neoatherosclerosis is higher in DES as compared to bare-metal stents (31 vs. 16%). The mechanism in DES can be explained since it reduces the capacity for re-endothelialization, leading to a neoatherosclerotic cascade with monocyte adhesion, neointimal migration, and increased permeability of the endothelium to circulating lipids, which end up migrating to the subendothelial matrix. This phenomenon is the main responsible for late catch-up, more common with DES. While the primary mechanism of bare-metal stents ISR is NIH, presenting clinically usually between the third and sixth month after PTCA, neoatherosclerosis most commonly occurs after the sixth month and is often symptomatic, because it is an injury with unstable morphological features (thin-layer fibroatheroma), very associated with acute coronary syndrome. Clinical differentiation with in-stent thrombosis is sometimes challenging.

Initially, neoatherosclerosis appeared to be a phenomenon only seen with first-generation DES, as a reaction to durable polymers. However, even with second generation DES, with biocompatible and even biodegradable polymers,
Accurate OCT resolution enabled the differentiation of ISR patterns, depending on the structure implanted. In bare-metal stent IRS, the characteristic pattern found is NIH, demonstrated by tissue with homogeneous hypersignal, rich in smooth muscle cells. In ISR of DES, the most commonly found pattern is neoatherosclerosis, which presents as a heterogeneous, multifaceted material with some characteristic aspects, such as intimal rupture, lipid lakes, thin-layer fibroatheroma, and macrophage agglomerates.

It is essential to define the ISR pattern found, and OCT also plays a key role in the morphological differentiation between ISR and in-stent thrombosis. Since neoatherosclerosis may manifest clinically as acute coronary syndrome, which may be due to ISR or thrombosis, the correct definition of stent failure with OCT may guide different forms of approach and treatment. For example, a neoatherosclerosis pattern in a poorly expanded stent area suggests that better expansion at high pressures, and optimization of stent deployment may lead to better long-term outcome. On the other hand, the presence of thrombus in an area of bad apposition suggests that the balloon or stent size to be employed needs to be revised.

Kang et al. demonstrated that in a series of patients presenting ISR in DES during a 32-month follow-up, 52% of lesions had at least one thin-layer fibroatheroma, 58% in-stent neointimal rupture, and 58% intraluminal thrombus, rendering understandable the unstable clinical presentation of these patients.

**TREATMENT OF RESTENOSIS**

The treatment of ISR still presents obstacles and challenges. Although the use of bare-metal stents has been drastically reduced in developed countries, its use in Brazil and in emerging countries is still frequent due to economic reasons, even with high failure rates. The wide introduction of DES significantly reduced the occurrence of ISR, since it interfered with the NIH process, a major cause of restenosis after stent implantation, directly impacting the clinical need for another revascularization.

The evolution of these devices brought greater efficacy and safety. Nevertheless, even with the advance of platforms, polymers and drug elution, these devices still cause ISR, which occurs in just over 10% in several clinical series.

**TREATMENT MODALITIES**

**Balloon angioplasty**

Plain old balloon angioplasty (POBA) was one of the first methods used to treat ISR. Although it is a method of treatment with easy applicability and good acute results, POBA has favorable results only in patients with focal ISR. In patients with diffuse ISR, there is often recurrence, especially in diabetic patients.

By and large, when this treatment modality is employed, some premises must be obeyed: dilate only the
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Angioplasty with cutting/scoring balloons

Cutting balloons are another option for treating ISR and they have the advantage of not sliding longitudinally (watermelon seeding), preventing edge injury. Some initial small studies showed potential benefits as compared to conventional balloon angioplasty, but the RESCUT study, with 428 patients, showed no difference in clinical and angiographic results when making this comparison. In this study, only patients with bare-metal stents ISR were included.30

Scoring balloons are very similar to cutting balloons, but present greater flexibility and deployment capacity, with good results in selected cases, as found in some publications; however, they lack consistent and comparative randomized studies.31

Neointimal debulking: laser and rotational atherectomy

The techniques of neointimal ablation (debulking) aim at extrusion of the intimal tissue inside the stent using laser or mechanical atherectomy. The rationale for using these techniques proposes that, in cases of ISR in adequately expanded stents, removal of tissue that obstructs the arterial lumen would be more efficient than conventional balloon angioplasty, since this causes endothelial injury and potentiates the recurrence of proliferative response. Excimer laser showed good results in selected cases (Figure 4), although with lower ablative capacity than rotational atherectomy.32

Rotational atherectomy was evaluated as treatment of ISR in bare-metal stents by means of randomized trials. The ROSTER study demonstrated that in diffuse ISR, excluding cases of underexpansion of the stent using IVUS, the use of rotational atherectomy reduced the rate of target lesion revascularization (TLR) as compared to POBA.33 The ARTIST study, in turn, despite being more robust in number of patients, failed to demonstrate superiority of rotational atherectomy in comparison to balloon, even presenting unfavorable short- and long-term results.34 Atherectomy should, therefore, be reserved as a treatment strategy of IRS only for cases with lesions where balloon dilatation is not possible, or else for neoatherosclerosis with significant calcification.

Bare-metal stents

When compared to conventional angioplasty, the use of bare-metal stents reduced ISR due to greater acute gain in relation to balloon. The phenomenon of acute luminal loss could result in better angiographic outcome in the long run. However, the immediate benefit was not followed by persistence in the late outcome. The RIBS I study compared 450 patients with ISR in BMS treated with balloon vs. angioplasty with bare-metal stenting. Although the immediate results were favorable to bare-metal stent, due to a greater acute gain, at the 6-month follow-up, the late luminal loss was significantly higher when compared to POBA. Minimal luminal diameter and stenosis diameter were not significantly different with both techniques after 6 months.35 Bare-metal stents should therefore be avoided in the treatment of ISR.36

Drug-eluting stents

DES have undoubtedly revolutionized the outcome of coronary angioplasty. If DES initially proved their efficacy in de novo lesions, it would be reasonable to apply them in the ISR scenario. The initial results with DES are observed in the long-run, unlike those with bare-metal stents. The first observational studies with first-generation DES demonstrated that they were safe and effective when used in ISR.37

The ISAR-DESIRE study compared the use of balloon with first-generation stents in the treatment of ISR. With 300 patients included, the ISR recurrence rates were 14.3% for patients treated with sirolimus-eluting stents, and 21.7% for those treated with paclitaxel-eluting stents, as compared to 44.6% in patients treated with balloon.38 In the RIBS II study, the treatment of ISR of bare-metal stent was significantly more effective with the use of siroli-
Drug-eluting balloons

Although the use of drug-eluting balloons remains controversial in native lesions, it showed to be effective in ISR in bare-metal stents or DES. Initially, better results were found as compared to the use of conventional balloons to treat ISR in bare-metal stents.44

A more challenging scenario is the comparison of drug-eluting balloons with DES in the treatment of ISR. The RIBS V study compared the use of drug-eluting balloons with second generation everolimus-eluted stents in the treatment of ISR in bare-metal stents.45 In that study, there was no statistically significant difference in the rate of ISR and clinical events in 1-year follow-up. Regarding angiographic outcomes, the minimum luminal diameter obtained with DES was larger when compared to the drug-eluting balloon (2.36mm vs. 2.01 mm; p<0.001).

A more current issue is the role of drug-eluting balloons in the treatment of ISR in DES. The efficacy of drug-eluting balloon in this scenario, compared to the conventional balloon, was initially demonstrated in a single center randomized study.46 The treatment of ISR in DES obtained better clinical and angiographic results with the use of drug-eluting balloon. The ISAR-DESIRE 3 study compared three different ISR treatment techniques: conventional balloon PTCA, drug-eluting balloon PTCA and angioplasty with DES. There were no differences in efficacy when comparing the uses of drug-eluting balloon and first-generation DES, both of which were better than conventional balloon.47

The PEPCAD clinical program confirmed good results using drug-eluting balloon as compared to a new angioplasty with DES in cases of ISR in DES.48 Other clinical studies confirmed these findings, raising the degree of recommendation of the use of drug-eluting balloon to treat ISR in DES.49,50 Although the use of a new DES may result in better acute luminal gain and consequent advantage in terms of angiographic outcomes, a learning curve using drug-eluting balloons to achieve favorable results in this scenario has been described. Careful preparation of the lesion with non-compliant balloons, and especially scoring balloons, prior to the use of the drug-eluting balloon results in a better angiographic result in the short- and long-run, as demonstrated in the ISAR-DESIRE study 4.52

Several advantages can be listed in the treatment of ISR in DES with drug-eluting balloons, instead of a new stent: it avoids multiple metal layers, reduces the time of antiplatelet use, enables new procedures, and may present lower thrombosis rates in the long run. The acute angiographic disadvantage can be minimized with adequate preparation of the lesion.

In sum, drug-eluting balloon angioplasty is an effective technique in the treatment of ISR in bare-metal stent and DES, being at least as effective as first-generation DES, without entailing additional deposition of metallic platform in the target vessel.

CONCLUSION

The advent of drug-eluting stents led to reduced cases of in-stent restenosis, but the increased use of new-generation drug-eluting stents in clinical practice still makes this complication relevant. In addition, today the in-stent restenosis cases are more challenging, because there is no consensus about the best strategy and treatment in this context. Biological and mechanistic phenomena may be involved. The former are immutable; the latter can be duly clarified and corrected.

Whenever possible, intracoronary imaging is key to elucidate the mechanism of stent failure, and may guide the new intervention to minimize this or other factors found. After the correct definition of the mechanism of in-stent restenosis, the use of drug-eluting balloons and new-generation drug-eluting stents is paramount in the therapeutic armamentarium, and coronary artery bypass graft is an option to be reserved for patients with in-stent restenosis associated with complex multivessel disease.

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CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF THE AUTHORS

Conception and design of the study: CNZ and MR; data collection: CNZ and MR; data interpretation: CNZ and MR; writing of the text: CNZ and MR; approval of the final version to be published: CNZ and MR.

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