FROM STENOSIS TO RESTENOSIS - THE NEW CORONARY ARTERY DISEASE CONTINUUM IN THE PCI ERA

Alice Elena Munteanu, Liviu Chiriac, Filip Romi Bolohan, Daniel Niță, Corina Diaconescu, Iulia Theodora Ionită, Mihnea Casian
“Dr. Carol Davila” Central Military Emergency University Hospital, Bucharest, Romania - Center of Cardiovascular Diseases, 2nd Department of Cardiology
Corresponding author: Munteanu Alice Elena, dralicepopescu@yahoo.com

Abstract
Mortality rates from acute myocardial infarctions have been declining in the past 4 decades since percutaneous coronary interventions (PCIs) became a valid therapeutical option. PCI is a non-surgical revascularization procedure in which blood flow in an occluded or narrowed epicardial coronary artery is re-established by inflating an angioplasty balloon in order to remove the blockage, followed by the insertion of a stent in order to maintain the patency of the artery. Since the late ’70s when the first bare metal stents (BMS) became available, progress has been made in developing new types of stents in order to lower the incidence of two important and feared complications: thrombosis and restenosis.

While thrombosis is manageable and preventable with antithrombotic therapy, restenosis is a more complex issue of which many clinicians may not be aware or underestimate. The review would like to summarize the current knowledge from the literature on stent restenosis and present to clinicians some tools for recognizing, or at least suspecting, restenosis in their patients.

Keywords: STEMI, stent, PCI, restenosis, coronary artery disease (CAD).

Rezumat
De la introducerea pe scară largă a intervențiilor percutane de revascularizare miocardică acum mai bine de 40 de ani asistăm la o scădere a mortalității în infarctul miocardic acut. Tehnica presupune restabilirilea fluxului coronarian normal prin dilatarea segmentului arterial stenozat sau ocluzionat cu ajutorul unui balon de angioplastie și, în cele mai multe cazuri, introducerea unui stent care asigură și menține patența vasului dilatat. Primelor stenturi metalice folosite la finalul anilor ’70 li s-au adăugat cu timpul noi tipuri de stent, al căror scop este de a preveni complicațiile ce pot surveni la nivelul stentului implantat, anume tromboza și restenoza.
Introduction

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, with myocardial infarction and stroke accounting for almost 80% of the entire cardiovascular related deaths\(^1\). However, for the past 4 decades we have been witnessing a decline in mortality from coronary artery disease (CAD) and stroke thanks to newly established protocols and dedicated therapies. Worldwide, almost 3 million people undergo the life-saving procedure of percutaneous angioplasty and stent implantation every year\(^2\). Since its introduction in 1977 as an alternative to surgical revascularization and thrombolytic therapy, it is currently the method of choice for acute coronary syndromes (especially STEMI) and most of the chronic coronary syndromes, saving many people from life-threatening complications in a manner which is both safe and effective. Most importantly, the 30 days mortality rates for patients with STEMI dropped to 2.5-10% thanks to the treatment of culprit lesions with percutaneous coronary intervention\(^3\). Coronary artery disease (CAD) is in fact a continuum of subclinical and clinical situations, which includes atherosclerotic plaque accumulation in the epicardial arteries, asymptomatic coronary artery stenosis, chronic coronary syndromes (CCS) such as “stable” angina and acute coronary syndromes (ACS) - unstable angina and acute myocardial infarction: NSTEMI and STEMI. Therefore, CAD is a chronic and progressive process, even in clinically apparently silent periods. Normally, a patient with CAD will undergo PCI when a hemodynamically significant stenosis is detected by an elective coronary angiography or in the setting of acute coronary syndromes in order to restore coronary blood flow and correct myocardial ischemia. However, as CAD is a dynamic process and even if the adequate medical...
therapy aims to slow its evolution, it will continue to generate new lesions and stented vessels are no exception. Therefore, restenosis is possible in some cases and should be regarded as another stage in the CAD continuum, especially in the present times when PCIs are more common than ever.

What is restenosis?

In-stent restenosis (ISR) is a new type of complication which arises in patients who previously underwent angioplasty and/or stent placement. It is clinically defined as a stenosis greater than 50% in a previously treated coronary artery segment with at least one of the following signs or symptoms: recurrent angina, ECG changes in the territory of the treated vessel at rest or in the setting of exercise stress test. However, in asymptomatic patients, a target lesion revascularization (TLR- repeat PCI of the target lesion performed because of a suspected complication) which shows a stenosis >70% in the previously treated coronary artery segment is also considered restenosis. Restenosis usually occurs in the first 3-9 months after PCI, being more frequent after 3-4 months\(^4\). In the case of bare-metal stents (BMS), late restenosis may occur after 4 years\(^5\). Apart from being a complication, ISR was also found to be an independent predictor for mortality during follow up, along with other relevant clinical factors (diabetes mellitus, left ventricular ejection fraction, smoking)\(^6\).

Is restenosis that common?

ISR is probably underestimated and it varies with the type of procedure. In the pre-stent era it ranged between 32-55% of all angioplasties and dropped to almost 17-41% in the BMS era\(^7\). With the advent of second-generation DES restenosis rates were significantly reduced to less than 10%\(^8\). The main difference between BMS and DES is that in addition to the metal structure, DES are coated with a polymer that emits an antimycotic/ antiproliferative drug (sirolimus, tacrolimus, everolimus, paclitaxel) which counterbalances the excessive neointimal proliferation occurring in presence of metallic struts. The issue with the first generation DES is that because their polymer coating remained intact on the struts, late and very late thrombotic events occurred (after 4 years or more)\(^9\). Therefore, the polymers used to coat the second generation DES are more biocompatible and biodegradable than the ones used in first generation DES in order to lower the rate of late thrombotic events. Risk factors associated with ISR are divided into 3 major categories: patient related, lesion related and procedural related (see Table 1). The most important clinical factor is diabetes mellitus (DM), specifically insulin- dependent diabetes mellitus\(^9\). It determines and fosters a prothrombotic state, with a decrease in the activity of antithrombin II and an enhanced platelet aggregation. In addition, insulin-like stimulatory growth factors promote a greater degree of neointimal hyperplasia. Therefore, in patients with DM and DES the restenosis rate was 21%, 6% higher than in their non-diabetic peers\(^10\).

Proposed pathogenic mechanisms for restenosis

It is important to think of restenosis as a progressive (or chronic) phenomenon, not as an acute complication, which is the case of stent thrombosis. Restenosis is triggered in
the first hours following PCI by barotrauma and leads to gradual narrowing of the stent lumen. The three major pathogenic mechanisms are: elastic recoil, vascular remodeling and neointimal hyperplasia. While the first two mentioned mechanisms are secondary to the balloon angioplasty, neointimal hyperplasia is induced by the metallic struts of the stents. Therefore, ISR is basically a non-specific perpetuated inflammatory response of the vessel wall in the setting of a persistent "insult" – the metal struts of the stent. DES combat vascular smooth muscle cell proliferation, migration and activation. Specifically, everolimus coated DES were found to dramatically reduce the rates of restenosis, thrombosis, TLR and acute myocardial infarction.

Clinical findings in restenosis

The diagnosis of angina is a clinical one and clinicians should always investigate chest pains with further questions, bearing in mind the main features of ischemic chest pain: character (constriction), duration (3-15 minutes), relation with effort (triggered by/ intensity decreases at rest) and response to nitroglycerin. In some cases, angina may not be present, but clinicians should always screen patients for its equivalents: dyspnea, diaphoresis, extreme fatigue or atypical pain. As in the case of CAD, the clinical presentation of patients with ISR is variable, ranging from silent ischemia, recurrent angina, acute myocardial infarction or even sudden cardiac death (SCD). However, taking into consideration that restenotic lesions are made up of neointimal hyperplasia and fibrous tissue, some authors consider it more stable than a regular atherosclerotic plaque. Therefore, patients with restenosis are more likely to have recurrent angina (CCS) rather than acute myocardial infarction (AMI) or SCD (which occur more frequently with stent thrombosis).

On the other hand, AMI can occur in 10% of these patients and ACS are more frequent than CCS in the first year following the procedure. Interestingly enough, DES were more frequently associated with ACS (4.3%) than BMS (1.6%). Up to 50% of patients with angiographic restenosis have no clinical symptoms. Although silent ischemia and atypical pains are more frequent in patients with DM, in this particular case DM was not associated with asymptomatic restenosis. On the contrary, restenosis in diabetic patients was associated with more severe symptoms, possibly because DM impairs the development of collateral coronary vessels. As a general observation, chest pain which occurs shortly after PCI (up to one month) is much more likely to be caused by thrombosis, while developing angina one
| Patient related          | Lesion related            | Procedure related               |
|------------------------|---------------------------|---------------------------------|
| Age                    | Lesion length             | Stent type (BMS/DES)            |
| Female sex             | Ostial lesions/ bifurcation| Number of stents                |
| Diabetes mellitus      | Small vessel              | Length of stents                |
| Genetic factors        | Multivessel CAD           |                                 |

*Table 1. Responsible factors of ISR*[^1]

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*Figure 1. Algorithm for diagnosing post PCI chest pain*[^2]
year after PCI is more likely because of restenosis. Thrombosis can also occur later (late: up to one year or very late: after one year) and can even complicate restenosis, with the two coexisting\(^{(17)}\). The two have a different prognosis: thrombosis is usually more severe (STEMI, SCD or even cardiogenic shock) and is associated with a higher mortality (20-40\%)\(^{(18)}\). There are other causes for chest pain following PCI, some of them include: “stretch” pain, microvascular angina, coronary artery spasm or incomplete revascularization (residual lesions).

**Tools for diagnosing restenosis**

A 12-lead rest ECG is mandatory in all patients, but it does not exclude CAD if normal. It may reveal ST segment and T wave abnormalities (negative, symmetric) which are classic markers of myocardial ischemia, especially if chest pain is present. The ECG stress test fails to detect myocardial ischemia secondary to restenosis in a large part of patients, having a low sensibility (46\%) and a somewhat higher specificity (77\%) and its routine use in the follow-up of patients with PCI did not lower the risk of cardiovascular events (ADORE trial)\(^{(19)}\). Therefore, it could be useful only in patients with suggestive symptoms. The 24-hour ECG monitoring can be useful in detecting silent ischemia or arrhythmias which could be secondary to myocardial ischemia.

Coronary CT Angiography is currently recommended for ruling out restenosis in the case of stents longer than 3mms or the ones found on the left main coronary artery\(^{(20)}\). Coronary angiography remains the pivotal diagnostic method. Fractional flow reserve (FFR) is a technique used in coronary catheterization to estimate pressure gradients across a coronary artery stenosis and determines if the stenosis impedes oxygen delivery to the myocardium. Coronary flow reserve (CFR) is the ratio between the maximal coronary blood flow and the resting coronary blood flow. A short and comprehensive algorithm for the diagnosis of restenosis in patients with post-procedural chest pain is detailed in figure 1.

**Treatment options**

The medical treatment in restenosis addresses the underlying pathogenic mechanisms: antiplatelet therapy (aspirin, clopidogrel, ticagrelor, prasugrel), anti-inflammatory drugs (corticosteroids, cilostazol), antiproliferative drugs (sirolimus)\(^{(22)}\). All patients who undergo PCI receive dual antiplatelet therapy for one year and statins, which have pleiotropic effects. Interventional treatment options include the following: balloon angioplasty (plain balloon, “cutting” balloon, “scoring” balloon, drug eluting balloon for BMS), the sandwich
technique (implanting another stent inside the already implanted stent after the balloon angioplasty), intracoronary brachytherapy or rotational atherectomy. The standard treatment for restenosis in DES is the sandwich technique, with the second DES being coated with the same active substance as the former or with a different one. It is worth mentioning that the recurrence rate of restenosis after treatment is almost two times higher in DES than in BMS\textsuperscript{[22]}. Coronary artery bypass grafting (CABG) is another option, particularly in patients with long restenosis, complicated coronary artery anatomy, progressive CAD or recurring restenosis.

Conclusions and take-home messages

It is now more common than ever to come across patients who underwent PCIs for CAD, regardless of the medical field. Internists should understand the different complications which can occur in these patients and screen them accordingly in order to refer them to a specialist if they have the clinical suspicion. Restenosis is generally underestimated. On one hand, clinicians consider that patients who underwent PCI are “cured”, which is not true considering the CAD continuum, and on the other, patients are less likely to complain about recurrent chest pains since most of them are used to it. The following ideas are what the authors consider to be the most relevant for clinicians in their everyday activity:

- Restenosis is a chronic, progressive complication which typically causes recurrent angina, while thrombosis is an acute, life-threatening complication.
- Restenosis typically occurs between 3 to 9 months after PCI, but in the case of BMS and first generation DES, it can occur even after 4 years.
- Diabetes mellitus is associated with higher rates of restenosis and more severe symptoms.
- In patients who previously underwent PCI, clinicians should always ask about chest pains and further investigate them by asking more questions in order to establish the probability of angina.
- Clinicians should be aware that restenosis is treatable and should refer suspected patients to specialists.

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