Restenosis of the Coronary Arteries

Past, Present, Future Directions

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KEYWORDS

• Restenosis • Coronary arteries • Neointimal hyperplasia • Progressive narrowing

KEY POINTS

- Restenosis, a pathologic response to injury, leads to narrowing of a stented vessel segment due to negative vascular remodeling and neointimal proliferation of vascular smooth muscle cells.
- Restenosis remains the most common cause of target lesion failure, and its predictors include diabetes, smoking status, female gender, acute coronary syndrome, previous percutaneous coronary intervention, saphenous vein graft disease, small vessel diameter, long lesions, high angiographic complexity, ostial location, and chronic total occlusions.
- The diameter achieved at the end of the procedure is an important modifiable predictor of restenosis.
- The prevention and optimal treatment of restenosis depend on several angiographic and clinical features and thus require an individualized approach.

BACKGROUND

Coronary artery restenosis, an exuberant response to mechanical injury of the arterial segment leading to lumen loss after percutaneous intervention, has plagued cardiologists since the introduction of balloon angioplasty by Gruntzig[1] and continues to do so despite contemporary drug-eluting stent (DES) technology. This article describes the mechanisms, clinical features, impact, and treatment options of restenosis after percutaneous coronary intervention (PCI).

Definition and Incidence

Obstruction of 50% or more of the diameter of a stenosis within 5 mm of a previously treated coronary segment is historically defined as binary angiographic restenosis.[2] Clinically driven restenosis rates are typically half that of binary restenosis.[3] Late loss (LL), a continuous angiographic measure of lumen deterioration, is calculated by subtracting the minimal luminal diameter (MLD) value at follow-up from postprocedural MLD. LL has traditionally served as a major outcome measure in bare-metal stent (BMS) trials and continues to play a similar role in the era of DES.[4,5] However, advanced imaging techniques, such as intravascular ultrasound (IVUS)[6] and optical coherence tomography (OCT),[7,8] are increasingly the modality of choice for quantitative assessments of neointimal thickness, neointimal volume, and minimal lumen diameter MLD (see Fig. 2).

Restenosis after BMS may present itself in the form of acute coronary syndrome in up to one-third of the patients,[9,10] whereas asymptomatic patients with nonfunctional angiographic restenosis typically experience a benign course.[11] Thus, target lesion revascularization (TLR),

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defined as any repeat percutaneous intervention of the treated coronary segment or bypass surgery of the target vessel, has been proposed as the most specific clinical restenosis end-point among other clinical markers (ie, death, myocardial infarction, symptoms recurrence, or combined major adverse cardiac events [MACE]).[12] Target vessel revascularization (TVR) expands the definition of TLR to include repeat percutaneous intervention of the target vessel, irrespective of the location of the stenosis within the treated segment. Target lesion failure (TLF) includes TLR, death, or myocardial infarction.

Thus, one should consider differences in time of follow-up assessment, percentage of patients with angiographic follow-up versus clinically driven data, and the patient population when interpreting clinical trial restenosis data. The incidence of LL and binary restenosis in key stent clinical trials is described in Table 1.[5,13–24]

MECHANISMS OF RESTENOSIS

Normal Versus Pathologic Response to Arterial Injury

The initial consequences of balloon angioplasty or coronary stenting are endothelial denudation, mechanical disruption of atherosclerotic plaque, often with dissection into the tunica media and occasionally adventitia, and stretch of the entire artery.[25] Endothelial injury, platelet aggregation, inflammatory cell infiltration, release of growth factors, medial smooth muscle cell (SMC) modulation and proliferation, proteoglycan deposition, and extracellular matrix (EMC) remodeling are the major milestones in the temporal sequence of the response to this trauma. In most patients, the healing response includes re-endothelialization of the artery without significant reduction in vessel diameter.

Restenosis is a pathophysiologic version of this response to injury, which leads to narrowing of the vessel segment due to negative vascular remodeling or neointimal hyperplasia (NIH)[26] (Fig. 1). NIH is initiated by multiple factors. The loss of a functional endothelium contributes NIH; endothelial injury alone is sufficient for the development of NIH in animal models,[27] through mechanisms that may require cytokine such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) to induce migration and proliferation of vascular smooth muscle cells (VSMC).[28] Platelet activation and deposition have been shown to occur almost immediately after endothelial injury in vivo[29,30] and also leads to PDGF production. Clinically, elevated platelet reactivity measured at the time of PCI has been associated with increased restenosis rates after balloon angioplasty.[31]

Endothelial Injury, Platelet Activation, Inflammation

In animal models, endothelial injury is sufficient for the development of NIH. Several mechanisms appear to directly link endothelial activation or denudation to restenosis. First, nitric oxide–mediated responses to flow and shear stress provide a protective response. Therefore, endothelial injury leads to the production of cytokines such as PDGF and TGF-β, which can induce migration and proliferation of VSMC.[28]

Endothelial response to injury also promotes platelet adhesion. Platelet activation and deposition have been shown to occur almost immediately after endothelial injury in vivo[29,30] and results in platelet production of cytokines and growth factors, including PDGF. Elevated platelet reactivity measured at the time of PCI has been associated with increased restenosis rates after balloon angioplasty.[31]

Inflammatory cell activation may also induce restenosis.[32] Innate immune responses, which have a predominance of monocyte/macrophage infiltrates, have been described. Antigen-specific adaptive immune hypersensitivity responses typified by infiltration of T cells and B cells in conjunction with eosinophils may also play a role in restenosis (reviewed in Ref.[33]).

However, the mechanisms that account for the most proximate fork in the road between a nonproliferative healing pattern and one ending in NIH are incompletely understood.

Smooth Muscle Cell Migration, Proliferation, and Extracellular Matrix Formation

Regardless of the precise initial steps, NIH ultimately results from both the inappropriate migration and the uncontrolled proliferation of VSMC (Fig. 2). VSMCs from the media and adventitia migrate into the intimal layer in response to PDGF[34] and are aided by fracture of the internal elastic membrane. Adventitial myofibroblasts also proliferate and migrate into the neointimal.[35] These cells shift from a contractile to the synthetic phenotype. In classic BMS restenosis, VSMCs proliferate from 24 hours to 2 to 3 months after vascular injury, returning to a contractile phenotype after this period. Analysis of atherectomy specimens suggests that monocyte/macrophages also proliferate within human in-stent restenotic tissue.[36]

Although cellular division is essential for the subsequent development of restenosis, so too is the synthesis of various collagen subtypes