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Restenosis Following Coronary Angioplasty: Current Status

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INTRODUCTION

Since introduction almost 25 years ago by Dr. Andreas Gruentzig, percutaneous transluminal coronary angioplasty (PTCA) has established itself as a viable non-surgical treatment option for patients with symptomatic coronary artery disease. With improvement in operation techniques and angioplasty equipments, especially with the availability of stents, the PTCA procedural success rate approaches over 95% in most lesions and complication rates around 1%. This remarkable procedural success, however, has not translated into sustained long-term outcomes. Restenosis or renarrowing at the site of successful PTCA has been the major limitation of this therapy since its inception. However, we now understand the mechanisms responsible for the restenosis process and have made tremendous progress in reducing the restenosis rates (Table 1). This review paper will highlight these strategies to combat restenosis.

Table 1. Mechanisms of restenosis and potential treatments

Mechanism	Treatment	Availability
Acute Recoil	Stent	Yes
Thrombus Deposition	Antiplatelet therapy including glycoprotein IIb/IIIa inhibitors	Yes
Inflammation	Anti-inflammatory agent	Yes
Chronic Geometric Remodeling	Stent	Yes
Neointimal Hyperplasia	Antiproliferative agent/drug-eluting stent	Undergoing investigation
In-stent neointimal hyperplasia	Brachytherapy	Yes

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RESTENOSIS: PAST

In the era of balloon angioplasty, restenosis was a frequent event, occurring in approximately 50% of patients by follow-up angiography and in about 30% of patients clinically within six months following a successful procedure[1, 2]. The mechanism of restenosis, based on limited animal studies in normal vessels and human autopsy findings, was felt to be initial thrombus formation and subsequent neointimal hyperplasia[3-6]. This partially correct assumption led to numerous pharmacological studies targeting reduction in thrombus deposition or neointimal hyperplasia. These investigations were initially conducted in animal models of overstretch balloon injury and when the results were positive, subsequently in patients. Although the animal studies were in general encouraging, the results of randomized clinical studies were uniformly disappointing[7]. The negative results were then felt to be a dosing issue, as the weight-adjusted drug dosage was at least a log order higher in animals. Similar amounts in patients would have resulted in severe systemic side effects. Thus, there was an intense interest and research into local drug delivery. The hypothesis was that the amount of drug necessary for preventing restenosis if given systemically would be toxic to the patients, but a smaller amount of the drug delivered at the site of angioplasty using these local drug delivery catheters would provide greater efficacy[8]. This approach also failed, because the drug delivery was inefficient (less than one percent of the drug was successfully delivered to the vessel wall) and the deposited drug did not stay around for a sufficient period of time for efficacy. More importantly, these therapies were based on incorrect assumption regarding the predominant mechanism of restenosis. Finally, the initial suboptimal results, not too infrequent after balloon angioplasty, also contributed to the high restenosis rates.

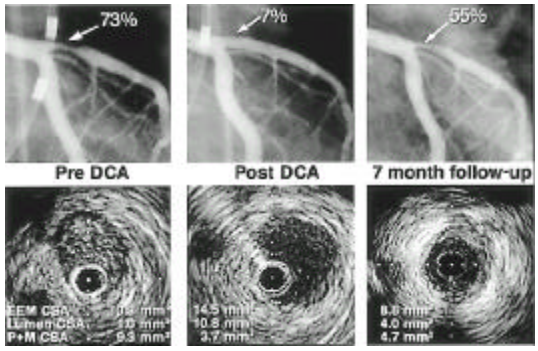

Figure 1. Angiographic (top panels) and intravascular ultrasound (bottom panels) findings in a patient with ostial left anterior descending coronary artery lesion (Left panels). The lesion was successfully treated with directional coronary atherectomy (DCA; Middle panels). However, seven months later, the patient returned with recurrent symptoms and restenosis (Right panels). Intravascular ultrasound demonstrated chronic geometric remodeling as the predominant mechanism of restenosis rather than neointimal hyperplasia. (Reproduced by permission from reference 7).

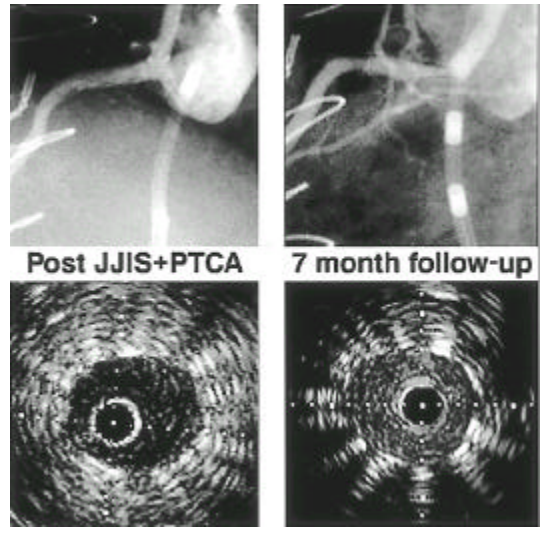

Figure 2. The ostial right coronary artery lesion was successfully treated with a Palmaz-Schatz stent (JJIS; Left panels). When the patient returned with restenosis (Right panels), intravascular ultrasound showed no change in stent dimension but severe neointimal hyperplasia as the cause of the in-stent restenosis. (Reproduced by permission from reference 7).

Thus, new angioplasty devices, such as directional coronary or rotational atherectomy catheters, were developed with the hope of modifying the plaque and reducing restenosis with a mechanical approach[9-11]. The results of randomized trials comparing the new angioplasty devices versus balloon angioplasty were also negative[12, 13]. Not until the seminal intravascular ultrasound (IVUS) observations of chronic geometric remodeling (vessel shrinkage at the site of angioplasty) being the predominant mechanism of non-stent angioplasty restenosis[14] did we begin to understand how to address the prevention of restenosis in a logical manner (Figure 1). It became clear that a mechanical approach with vessel scaffolding, such as the metallic stents, was the only way to prevent chronic vessel shrinkage. Indeed, the randomized trials comparing the Palmaz-Schatz stents versus balloon angioplasty were the first clinical restenosis studies to provide positive results[15, 16]. However, even these encouraging results showed that stents reduce but do not eliminate restenosis. Subsequent studies in unfavorable lesions, such as small vessels (<3.0 mm in diameter) or diffuse lesions (>10 mm in length), showed that stents are still associated with high restenosis rates, not too dissimilar from those after balloon angioplasty[17, 18]. Furthermore, IVUS observations in patients documented that in-stent restenosis is purely neointimal hyperplasia[19], as stents do not recoil over time (Figure 2). Thus, investigators have attempted to define the variables associated with in-stent restenosis. These studies, especially with the aid of IVUS, showed that ostial location, pre-intervention plaque burden and post-intervention lumen dimensions assessed by IVUS[20], and diabetes mellitus[21] were predictors of eventual in-stent restenosis. Thus, the stent implantation techniques evolved to high-pressure adjunct balloon angioplasty to optimize the initial stent implantation[22]. However, refined techniques still cannot modify the restenosis rates at the ostial location or in diabetic patients. Furthermore, for those lesions not amenable to stent implantation, the restenosis rate is still unacceptably high.

RESTENOSIS: PRESENT

It is clear that stents are the only angioplasty device to have an impact on restenosis. However, there are still unfavorable lesion subsets, such as small vessels, diffuse lesions, ostial lesions, saphenous vein graft lesions and diabetic population whose restenosis rates have not been altered by stents. Especially for these lesions, new approaches, such as drug-coated stents and intravascular brachytherapy, are actively investigated to reduce restenosis.

The most exciting development has been the drug-coated stents. The rationale for this approach is that the metallic stent would provide the scaffolding to prevent geometric remodeling and that the antiproliferative agent impregnated on the stent platform would prevent neointimal hyperplasia, thus addressing both mechanisms of restenosis with the same device. Despite the theoretical difficulties of finding biocompatible polymers for drug impregnation, drugs effective at low dose, and unknown pharmacokinetics, there have been encouraging animal studies[23, 24]. Based on these results, the rapamycin-coated stents have been studied in 30 patients with de novo single vessel disease[25]. The results of this preliminary registry study have been astounding, with no angiographic or clinical restenosis at one-year follow-up. This stent as well as other drug-eluting stents, such as paclitaxel-coated stents and actinomycin-eluting stents, are undergoing randomized trials against bare metal stents to determine the efficacy of this approach for the prevention of restenosis. Whether this therapy would be effective in unfavorable lesions is not known.

Another novel approach, which has been more successful in treating the in-stent restenosis than the prevention of restenosis for de novo lesions, is the intravascular brachytherapy[26]. The mechanism of brachytherapy is that the ionizing radiation would prevent the dividing cells, such as the smooth muscle cells causing the neointimal hyperplasia, from proliferation by damaging the nucleus of the cells. Several randomized trials have documented the beneficial effect of this approach with both gamma[26-28] and beta radiation in reducing the recurrent in-stent restenosis[29]. The preliminary result of the beta radiation for prevention of restenosis following angioplasty of de novo lesions has been discouraging[30]. However, whether gamma radiation or different beta system would prevent the initial restenosis, especially in combination with stents, needs further evaluation.

RESTENOSIS: FUTURE

Future efforts should try to prevent restenosis completely rather than merely reduce the rates. This may involve a combination of mechanical devices and adjunct pharmacology. The restenosis process is a culmination of multiple factors, including the initial thrombus formation, inflammation, geometric remodeling and neointimal hyperplasia. Potent pharmacological agents could prevent the first two processes, stents would prevent the third event and effective antiproliferative agents, ideally from the stent platform, could address the last process. Potentially more effective drug-eluting stent platform may be drug impregnation of stent grafts, as the graft material would allow impregnation of the drug in a much larger area (close to 90% of the lesion area versus 15-20% for bare metal stents). This device would have limited use in native coronary arteries, however, due to the presence of many side branches and the occlusion of these branches by the graft material.

Alternatively, the angioplasty procedure may have to prevent only the recurrence of ischemia in the target vessel, even if the angioplasty site should become renarrowed. This approach may involve the drug-eluting stent and administration of angiogenic growth factors or gene therapy to myocardium supplied by the treated vessel[31]. Thus, even if the stent should become restenosed, the angiogenesis in the target area may prevent the occurrence of ischemia and the need for repeat intervention.

CONCLUSIONS

The restenosis process is an uncontrolled progression of the natural healing process. Thus, therapies aimed at allowing the necessary healing to occur (i.e., re-endothelialization) and yet preventing the excess scarring (both adventitial and intimal) could prevent restenosis. With rapidly evolving technologies and continuing research, restenosis will be prevented in the majority of patients in the near future and the minority with restenosis still may benefit from a combination therapy aimed at preventing ischemia, not necessarily restenosis.

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