HULA-HOOPS, PET ROCKS AND INTRAVASCULAR BRACHYTHERAPY

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INTRODUCTION

During the past 25 years, we have seen dramatic changes in the management of patients with coronary artery disease. The introduction of coronary angioplasty, or balloon dilatation, by Gruentzig in 1977 heralded a fundamental breakthrough in the treatment of patients with obstructive coronary artery disease.1 Now termed percutaneous coronary intervention (PCI), more than one million patients per year are treated worldwide, making PCI the most commonly performed therapeutic procedure in adult medicine.2

Despite remarkable chronological developments that refined the safety and effectiveness of PCI, its Achilles heel was the vexing problem of restenosis, a rapid (within six months) growth of scar tissue, or neointima, within the PCI-treatment site. Most of the 25-35% of patients who experienced restenosis ultimately needed a repeat PCI or coronary bypass operation. In light of its frequent occurrence, restenosis limited the application of PCI to patients with predominately single- or double-vessel coronary artery disease.3

While hundreds of adjunctive medical therapies and specialized PCI catheter technologies such as laser and atherectomy were tested over the years in an attempt to curb restenosis, none were successful. The introduction of coronary artery stents vastly improved PCI safety, yet stenting resulted in only a minor reduction of restenosis.4

THE BREAKTHROUGH

For years it was known that excessive scar tissue formation after skin wound healing, commonly called keloid, could be prevented by radiation treatment. Presuming that restenosis was, in essence, excessive scar tissue formation within an artery following balloon or stem "injury," several researchers studied the intravascular delivery of radiation or intravascular brachycherapy (IVBT) in animal models of restenosis. Almost simultaneously, researchers from Columbia University, Emory University and our group at Baylor College of Medicine and the Methodist DeBakey Heart Center (including Ors. Wojciech Mazur, M. Nadir Ali, Greg Kaluza and Kam Chiu) demonstrated and reported IVBT's remarkable ability œ dramatically inhibit the rescenosis process (Figure 1).5

Clinical trials in humans were soon scarred. The PREVENT trial, with the Methodist

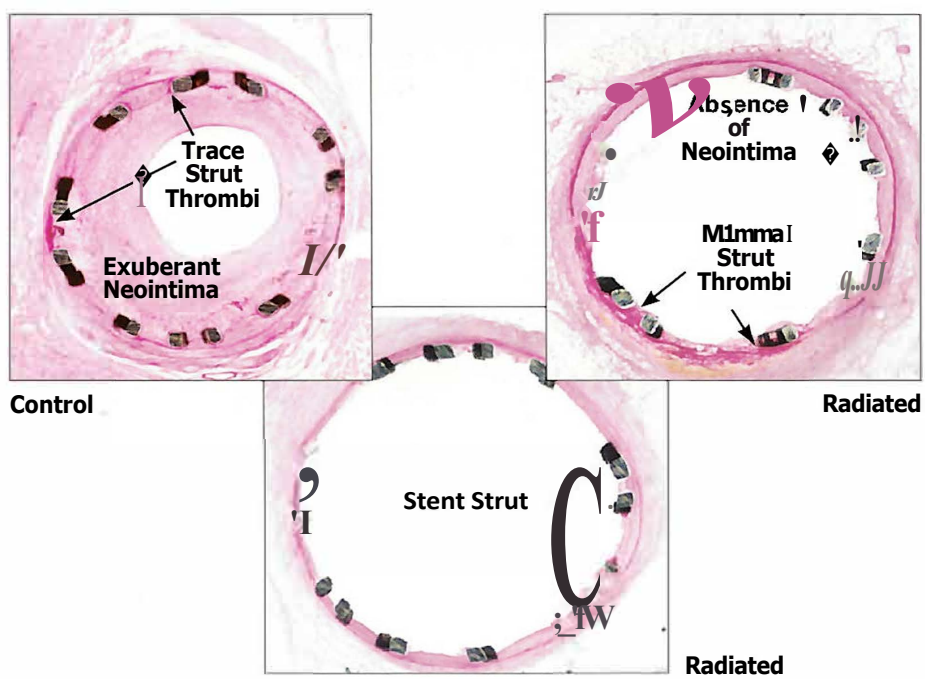

Figure 1.
Histologic sections of pig coronary arteries from one of the first studies of IVBT done at Baylor College of Medicine and the Methodist DeBakey Heart Center. The left panel shows control artery, which did not receive radiation therapy. Note the thick neointima and small, compromised lumen (clear space). The middle and right panels are from arteries that received radiation therapy. Note the absence of neointima and the large, uncompromised lumen.

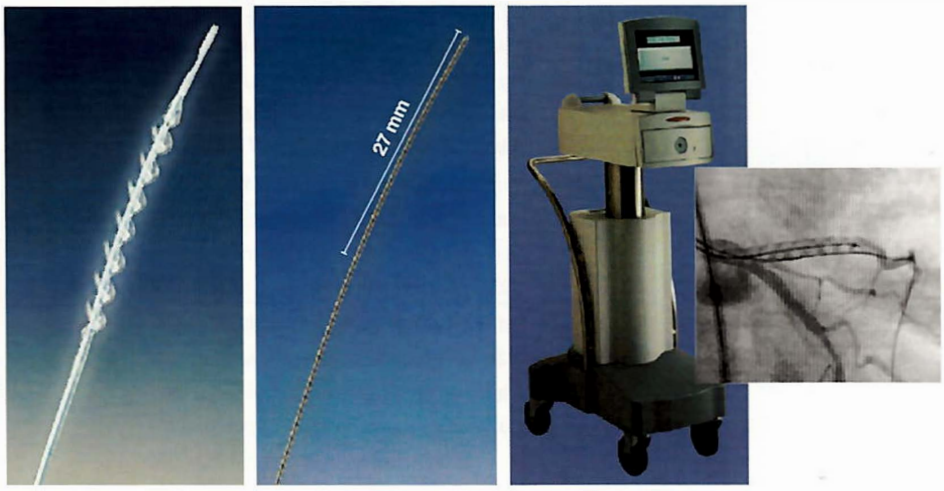

Figure 2.
The Guidant GALILEO® Intravascular Radiotherapy System was developed at the Methodist DeBakey Heart Center and used in the first patient. The system consists of a "centering catheter," which is placed in the coronary artery to be treated: a radioactive "source wire," which is inserted through the center channel of the centering catheter, and a "source delivery unit," which is connected to the centering catheter and automatically feeds and withdraws the source wire to and from the treatment site. This highly sophisticated system automates the IVBT process to minimize human error.

DeBakey Heart Center serving as lead institution, was one of the first pilot studies to demonstrate the safety and efficacy of IVBT in patients after balloon angioplasty or stent implantation.6 Subsequently, three large pivotal trials tested IVBT in patients who already had developed in-stent restenosis: GAMMA 1 (Cordis CheckMate™), which used gamma radiation (192Ir);[7] START (Novoste™ Beta-Cath™), which used beta radiation (90Sr);[8] and INHIBIT (Guidant GALILEO®), which used beta radiation (32P) (Figure 2).9 These studies provided conclusive clinical evidence of the effectiveness of IVBT in preventing recurrence of in-stent restenosis. IVBT soon became an important tool for interventional cardiologists as the first effective weapon against restenosis (Figure 3).

PROBLEMS WITH IVBT

As IVBT gained widespread use, specific problems and issues became apparent. Patients occasionally developed narrowing in the coronary artery at the edge of the radiation treatment, particularly if balloon dilatation had occurred beyond the created arterial segment. This so-called "edge effect," attributed to "geographic miss," occurred in approximately 10% of patients who underwent IVBT (Figure 4).10 Extending the length of radiation treatment to cover the entire injured area with a generous radiation margin has markedly diminished this problem.11

The potency of IVBT in inhibiting the artery's response to balloon or stent injury was also problematic because it slowed the normal "healing" process by which the artery repaired the site of dilatation or stenting. When complete, this healing process protected the artery from thrombosis. Cases of "late thrombosis" caused by delayed or incomplete healing, although uncommon, were reported and were of justifiable concern.[12] The prolonged use of antiplatelet drugs, aspirin and thienopyridines, like clopidogrel, for at least one year after IVBT seemed to effectively reduce this potentially serious complication.13

Finally, late follow-up studies of IVBT have shown the treatment to be durable but not permanent. Studies carried out up to five years have shown a trend towards late development of restenosis, called the "catch-up phenomenon."[14]

THE EMERGENCE OF DRUG-ELUTING STENTS

As IVBT proved that interfering with proliferating cells' DNA structure prevented the accelerated and uncontrolled growth of vascular tissue, other methods to interrupt the cell cycle were studied. Sirolimus (rapamycin, an anti-immune response drug) and paclitaxel (a chemotherapeutic drug) were ingeniously coated onto the stent surface and applied directly to the inner lining of the artery when the stent was deployed. In animal studies, pilot studies and pivotal randomized clinical trials - and now through extensive clinical experience - these drug-eluting stents have been shown to profoundly reduce restenosis. In the SIRIUS trial, the sirolimus-eluting stent (Cypher™, Cordis) reduced the need for repeat PCI of the same lesion, or target lesion revascularization, by 75% compared to patients treated with a non-medicated bare metal stent.15 Similarly, the paclitaxel-eluting stent (TAXUS™ Boston Scientific) reduced the need for target lesion revascularization by 75%.[16] Target lesion revascularization with the

drug-eluting stents was less than 5% in both trials, the *coup de grace* to the problem of restenosis.

At the Methodist DeBakey Heare Center, patients who required PCI for restenosis previously accounted for more than 10% of procedural volume. Such patients now have fallen to less than 2% of procedures. IVBT and now drug-eluting stents have provided a potent one-two punch against restenosis.

IVBT IN THE DRUG-ELUTING STENT ERA

Currently, the occasional patient with restenosis is treated with another drug-eluting scent. And, as with hula-hoops and pet rocks, IVBT essentially has come and gone.

As science and technology progress, better and beccer methods become available to treat patients with coronary artery disease. A breakthrough technology like IVBT establishes a revolutionary new approach, setting the stage for and ultimately being supplanted by even better therapies. As always, the ultimate winners in this revolution of medical advancement are our patients.

REFERENCES

1. *GruentzigAR, SenningA, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl] Med 1979.-301:61-68.*
2. *Arjomand H, Turi ZG, McCormick D, Goldberg S. Percutaneous coronary intervention: historical perspectives, current status, and fature directions. Am Heart]. 2003;146:787-796.*
3. *Lowe HC. Oesterle SN, Khachigian L M Coronary in-stent restenosis: current status and future strategies. J Am Coll Cardiol. 2002:39:183-193.*
4. *Serruys PW, Unger F, Sousa JE, fatene A, Bonnier HJ, Schonberger JP, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl] Med. 2001;344:1117-1124.*
5. *Kaluza GL, Mazur W, Raizner AE. Basic science review: radiotherapy for prevention of restenosis. Catheter Cardiovasc lnterv. 2001;52:518-529.*
6. *Raizner AE, Oesterle SN, Waksman R, Serruys PW, Colombo A, Lim YL, et al. Inhibition of restenosis with beta-emitting radiotherapy: report of the Proliferation REduction with Vascu/,ar ENergy Trial (PREVENT). Circu/,ation. 2000;102:951-958.*
7. *Leon MB, Teirstein PS, Moses JW, Tripuraneni P, Lansky A], Jani S, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. N Engl] Med. 2001;344:250-256.*
8. *Popmaj], Suntharalingam M, Lansky A], Heuser RR, Speiser B, Teirstein PS, et al. Randomized trial of 90Sr/90Y beta-radiation versus*

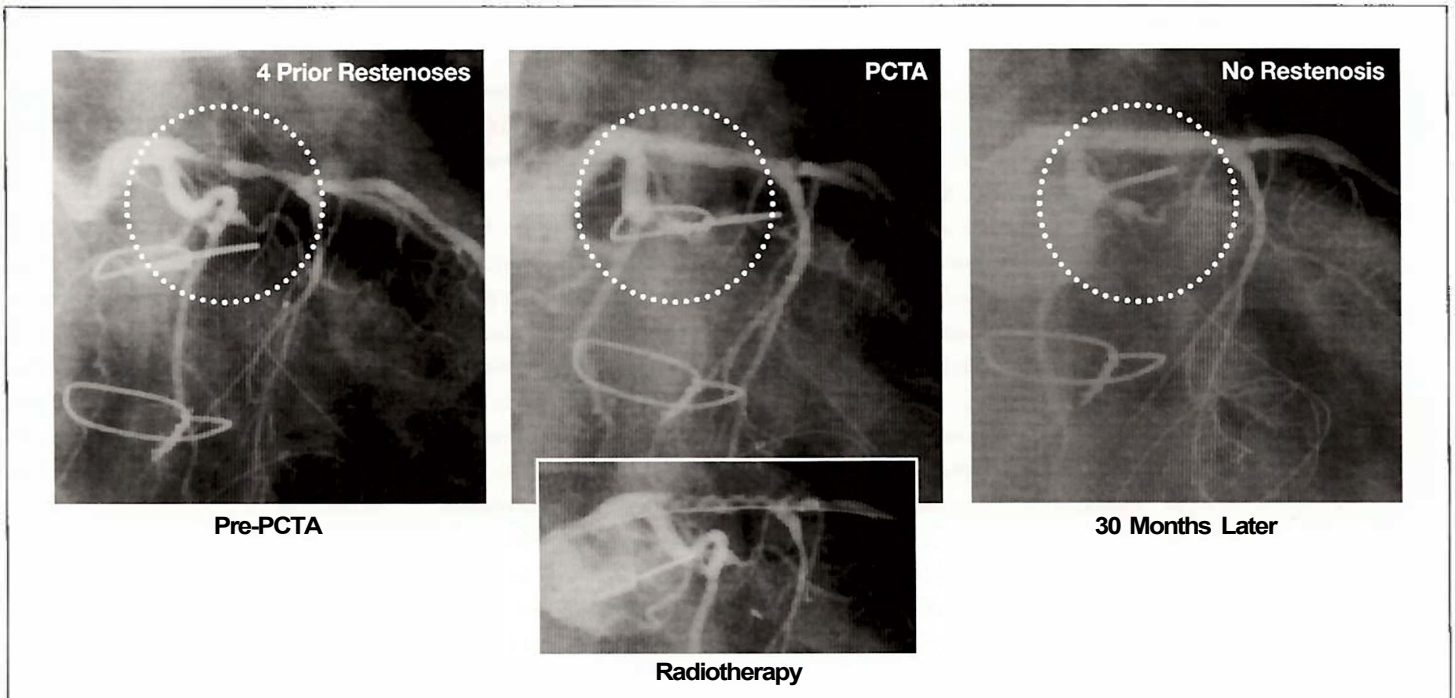

Figure 3.
These coronary angiograms are from a patient who, before MBT, underwent four prior angioplasties, each of which restenosed within six months. The left panel shows severe narrowing (within dotted circle) after the fourth of these unsuccessful attempts. The narrowed artery is redilated and treated with radiotherapy (center panels). Thirty months after MBT. the artery is still wide open, indicating the effectiveness of MBT to prevent restenosis (right panel).

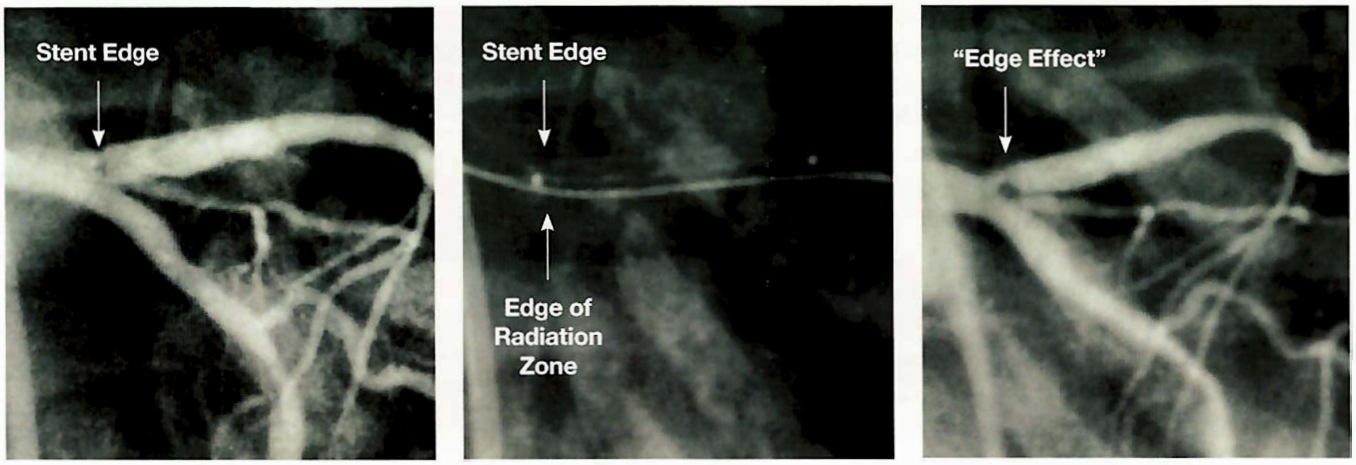

Figure 4.
An example of the "edge *effect."* one of the problems occasionally encountered after MBT. The left panel shows an open artery after stent placement. The center panel shows the radiation treatment with the treatment edge very close to the stent edge (i.e., no radiation margin). Six months later (right panel), the artery renarrows precisely at the treatment edge, the so-called "edge effect."

placebo control for treatment of in-stent restenosis. Circulation. 2002; 106:1090-1096.

9. *Waksman R, Raizner AE, Yeung AC, Lansky AJ, Vandertie L. Use of localised intracoronary beta radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. Lancet. 2002;359:551-557.*
10. *Sabate M, Costa MA, Kozuma K, Kay IP, van der Giessen WJ, Coen VL, er al. Geographic miss: a cause of treatment failure in radio-oncology applied to intracoronary radiation therapy. Circulation. 2000; 101:2467-2471.*
11. *Sianos G, Kay IP, Costa MA, Regar E, Kozuma K, de Feyter PJ, et al. Geographical miss during catheter-based intracoronary beta-radiation: incidence and implications in the BRIE study. Beta-Radiation In Europe. j Am Coll Cardiol. 2001;38:415-420.*
12. *Waksman R, Bhargava B, Mintz GS, Mehran R, Lansky AJ. Satler LF, et al. Late total occlusion after intracoronary brachytherapy for patients with in-stent restenosis. J Am Coll Cardio/. 2000;36:65-68.*
13. *Waksman R, Ajani AE, Pinnow E, Cheneau E, Leborgne L. Dieble R, et al. Twelve versus six months of clopidogrel to reduce major cardiac events in patients undergoing gamma-radiation therapy for in-stent restenosis: Washington Radiation for In-Stent restenosis Trial (WRIST) 12 versm WRIST PLUS. Circulation. 2002; 106: 776-778.*
14. *Grise MA, Massullo V. Jani S, Popma ff, Russo RJ, Schatz RA, et al. Five-year clinical follow-up after intracoronary radiation: rernlts of a randomized clinical trial. Circulation. 2002; 105:2737-2740.*
15. *Moses JW, Leon MB, Popma jj, Fitzgerald Pf, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349:1315-1323.*
16. *Stone CW, Ellis SC, Cox DA, Hermiller], O'Shaughnessy* C, *Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004;350:221-231.*