Current Status of Intracoronary Radiation Brachytherapy

On-Hing Kwok
Wing-Hing Chow
Ashley Chi-Kin Cheng

Follow this and additional works at: https://www.jhkcc.com.hk/journal

Recommended Citation
On-Hing Kwok, Wing-Hing Chow, Ashley Chi-Kin Cheng, Current Status of Intracoronary Radiation Brachytherapy Journal of the Hong Kong College of Cardiology 2001;9(4) https://doi.org/10.55503/2790-6744.1175

This Review Article is brought to you for free and open access by Journal of the Hong Kong College of Cardiology. It has been accepted for inclusion in Journal of the Hong Kong College of Cardiology by an authorized editor of Journal of the Hong Kong College of Cardiology.
Current Status of Intracoronary Radiation Brachytherapy

ON-HING KWOK, WING-HING CHOW, *ASHLEY CHI-KIN CHENG

From Division of Cardiology, University Department of Medicine, Grantham Hospital, *Department of Clinical Oncology, Queen Mary Hospital, Hong Kong

KWOK ET AL.: Current Status of Intracoronary Radiation Brachytherapy. Percutaneous coronary intervention has become the predominant mode of revascularization worldwide. However, its intermediate- and long-term efficacy is limited by restenosis, despite advances in pharmacological therapy, facilitated angioplasty and device synergy. Vascular radiation brachytherapy (VBT), after undergoing painstaking clinical trials and evaluations, has emerged as a viable treatment option to tackle the vexing problem of restenosis. Brachytherapy programs have been set up in heart centers throughout the world. The explosion of research in cardiovascular radiation medicine is overwhelming. However, vascular brachytherapy itself has brought about new problems, like late thrombosis, edge effects, late stent mal-apposition, etc. From the practical perspective, the issue of radiation safety, availability of on-site Radiation Oncologist and Medical Physicist, especially in the event of anticipated ad hoc procedures, and the cost-effectiveness of brachytherapy (taking into account the use of prolonged antiplatelet therapy) need to be addressed and resolved. Recently, new contenders in the field, drug-eluted stents in particular, have become the focus of both bench and bedside research, directly threatening the niche role of VBT in restenosis prevention. This brief review summarizes some of the basic concepts of VBT, results of clinical trials, local experience with this novel technique and future directions in restenosis prevention. (J HK Coll Cardiol 2001;9:176-183)

Angioplasty, brachytherapy, radiation, review, stent

Address for reprints: Dr. On-Hing Kwok
5/F Kwok Tak Seng Heart Center, University Department of Medicine, Grantham Hospital, 125 Wong Chuk Hang Road, Aberdeen, Hong Kong

Tel: (852) 2518 2619, Fax: (852) 2518 8558

Received June 19, 2001; revision accepted July 13, 2001

摘 要
經皮穿刺冠狀動脈介入性治療已成為全球血液重運的主要模式之一。然而，儘管藥物治療進展迅速，協助性血管成形術及新儀器的配合發展一日千里，仍未能解決血管成形術之後再狹窄的問題，至今經皮穿刺介入式治療中，長線的治療成效受到一定限制。經過長時期的仔細臨床實驗及評估後，冠狀動脈短距離放射治療終於成為解決再狹窄的有效方法之一。短距離放射治療已在全球多個心腦中心被廣泛應用，在心腦血管放射醫學方面的研究更是多不勝數。然而，血管放射治療本身亦衍生了新的問題，例如支架晚期栓塞、邊緣效應及晚期支架偏離血管壁等。從實際角度而言，輻射的問題，如何召集放射腫瘤科醫生及醫學物理學家到場進行即席放射治療，及治療的成本效益等等〈還要考慮到長期服用抑制血小板藥物的治療成本〉，都是需要進一步探討及解決的課題。最近，透藥性支架正成為動物及臨床研究的焦點，直接威脅到短距離放射治療在預防再狹窄方面的地位。本文總結了一些血管近距離放射治療的基本概念，臨床試驗結果，本地應用此技術的經驗及防治再狹窄方面的展望。

關鍵詞：血管成形術 近距離治療 放射性 回顧 支架

J HK Coll Cardiol, Vol 9 October 2001 176
CURRENT STATUS OF INTRACORONARY RADIATION BRACHYTHERAPY

**Introduction**

Endovascular stents were developed to buttress the artery against deforming stress. Nowadays stents are very effective in addressing the elastic recoil and negative remodeling after balloon stretch injury of vessels. However, neointimal hyperplasia after stenting remains the "Achilles heel" of contemporary percutaneous coronary intervention (PCI) despite advances in facilitated angioplasty and device synergy. The majority of lesions in real-world PCI belong to the "non-BENESTENT" type and therefore the down-to-earth restenosis rate is in the range of 30% to 50%, taking into account the diabetic subgroup, small vessels and complex lesion subsets. It has been estimated that reduction of target vessel failure rates by 10% could save 1 billion US dollars annually in the United States alone.

Vascular radiation brachytherapy (VBT), after undergoing painstaking clinical trials and evaluations, has emerged as a viable treatment option to tackle the vexing problem of restenosis. The approval from the US Food and Drug Administration (FDA) in November 2000 of both the Checkmate™ Iridium-192 (Johnson & Johnson/Cordis, Miami, FL) and the Beta-Cath™ Strontium/Yttrium 90 (Novoste, Norcross, GA) systems indicates that the field has now reached a level of maturity not previously attained. VBT programs have been booming all over the world, including Hong Kong. Meanwhile, recent release of promising clinical results of drug-eluted stent trials has heralded a major challenge to the niche role of VBT in restenosis reduction.

**Mechanism and Patterns of Restenosis**

Intravascular ultrasound (IVUS) studies have elucidated that about 70% of the late lumen loss after balloon angioplasty is due to negative vessel remodeling, whereas intimal hyperplasia accounts for the remaining 30%. On the other hand, stents virtually abolish negative remodeling, and instent restenosis (ISR) is solely the result of neointimal tissue proliferation though sometimes "pseudo" stent recoil due to stent under-expansion, stent "crush" or stent "misplacement" at the time of implantation may masquerade ISR.

Based on the extent and distribution of intimal hyperplasia, Mehran et al. has classified ISR into 2 major categories, viz. focal (≤10 mm in length) and diffuse (lesion length >10 mm), the latter of which carries a worse prognosis with one-year target lesion revascularization rate of over 50%.

**Vascular Injury and Repair**

The pathophysiology of restenosis reflects a paradigm of healing response of arteries that are injured by reconstructive techniques. It is comprised of contraction and fibrosis of the vessel wall known as remodeling, and an active growth of a fibrocellular lesion composed primarily of vascular smooth muscle cells (VSMC) and extracellular matrix. The adventitial cells are playing a pivotal role in the healing process. A number of growth factors are involved in the stimulation of VSMC during neointimal hyperplasia, including platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor beta (TGF-β), and angiotensin II. Activated VSMC have also been found to produce a variety of enzymes, cytokines, adhesion molecules and other proteins that not only enhance the inflammatory response within the vessel wall but also stimulate further vascular cell abnormality. This proliferative cascade has become the predominant target of clinical and experimental intervention in restenosis prevention.

**Biological Effect of Ionizing Radiation**

Radiotherapy has been well known for treating hyperplastic conditions like keloids. The rationale for its use in restenosis reduction is based on the enhanced sensitivity of actively proliferating cells to ionizing radiation. The predominant vascular response to radiation delivered at the therapeutic doses for VBT is chromosomal damage in the VSMC, fibroblasts and
when present, endothelial cells, resulting in the loss of the cells' ability to replicate with subsequent mitotic cell death. Bromodeoxyuridine (BrdU) labeling in balloon-injured porcine coronary arteries demonstrated that intravascular irradiation significantly reduced the percentage of proliferating cells in both the media and the adventitia. Radiation-induced apoptosis is known to occur in some tissues and its induction in the vessel wall could well be another mechanism for limiting neointima formation. However, Waksman et al. found no increase in apoptotic activities 3 to 7 days after radiation in the porcine overstretch injury model, whereas subsequent studies found delayed increase in apoptosis 14 days after VBT. Phenotypic modulation is evident after VBT. It appears that irradiation results in an inability of neointimal cells to acquire smooth-muscle specific $\alpha$-actin even by 6 months after angioplasty.

The Gamma Trials

SCRIPPS is the first randomized trial on the safety and efficacy of intracoronary gamma radiation for reducing coronary restenosis. In this study, 55 patients were randomized to receive placebo or Iridium-192 (8-30 Gy, dosimetry guided by IVUS) utilizing a ribbon source (19-35 mm), delivered in a non-centered closed-end lumen catheter at the treatment zone (dwell time 20 to 45 minutes). The study demonstrated 6-month angiographic restenosis rate of 17% in the treatment group vs. 54% in the placebo. (p<0.02; 70% relative reduction) There was no obvious complications or untoward adverse sequel from the treatment and the clinical benefits and safety were maintained beyond 3 years.

Subsequent clinical trials using gamma irradiation, which include WRIST (Washington Radiation for In-Stent Restenosis Trial), LONG-WRIST, SVG-WRIST, GAMMA-ONE, essentially demonstrated significant reduction of angiographic binary restenosis and major adverse cardiac events (MACE) by 30% to 50% in the irradiated arm versus the placebo arm in various lesion subsets. The dose range was 14-18 Gy at 2 mm. However, gamma irradiation was uniformly associated with a higher rate of late stent thrombosis, which warrant further investigation and solution.

The Beta Trials

The Beta Energy Restenosis Trial (BERT) was the first FDA approved trial of radiation for restenosis and was designed as a feasibility study to evaluate the safety and efficacy of intracoronary beta irradiation using the Beta-Cath™ system at doses of 12, 14 and 16 Gy at 2 mm from the source center in single de novo lesions less than 15 mm long. The study was started in Emory University. The source was Strontium/Yttrium 90 delivered hydraulically down a 5F passive-centering system. Angiographic follow-up at 6 months demonstrated a late loss of 0.05 mm, late loss index of 4% with a lower-than-expected restenosis rate of 15%. An expanded phase of the study has been carried out in the Montreal Heart Institute and the Thoraxcenter in Rotterdam.

Beta-WRIST registry trial was an open-label study evaluating the safety and efficacy of beta-radiation using Yttrium-90 (Boston Scientific/SCIMED), in 50 patients with in-stent restenosis. It showed that beta irradiation resulted in lower-than-expected rate of angiographic and clinical restenosis at 6 months. Verin et al. have demonstrated that intracoronary beta-radiation therapy produces a significant dose-dependent decrease in the rate of restenosis after angioplasty. An 18-Gy dose not only prevents the re-narrowing of the lumen typically observed after successful balloon angioplasty, but also induces luminal enlargement (positive remodeling).

START (STent And Radiation Therapy) trial is the largest, prospective, randomized, triple-masked, placebo-controlled (dummy-source) beta-radiation brachytherapy trial (using Strontium 90/Yttrium 90 Novoste™ Beta-Cath™ system) enrolling 476 patients. The study showed that Sr-90 reduced the primary clinical endpoint of target vessel revascularization by 34% (p=0.026) in patients undergoing treatment for in-stent restenosis. Target lesion revascularization was reduced by 42% (p=0.008) and major adverse cardiovascular event was reduced by 31% (p=0.039). Treatment with Sr-90 reduced recurrent restenosis by 36% in the entire analysis segment and by 60% in the stented segment. Delayed clinical stent thrombosis was not seen in the study, even with new stent implantation (with clopidogrel or ticlopidine prescribed for 60 to 90 days). Subsequent INHIBIT trial (n=332) using the Guidant™ Galileo™ Phosphorus-32 source wire with a centering spiral
balloon delivery catheter essentially showed similar reduction in angiographic binary restenosis and MACE in the irradiated arm vs. the placebo. Collectively, clinical studies suggested that catheter-based beta and gamma emitters appeared to be equally effective in reducing restenosis by 30% to 50% and recurrent events in ISR. However, there were great differences in the dose administered and lesion lengths treated in the various trials, rendering head-to-head comparison rather difficult.

De Novo Lesions

Use of VBT in primary prophylaxis of restenosis in de novo lesions is still controversial. The Proliferation Reduction with Vascular Energy Trial (PREVENT) is a small, randomized study using the Galileo P-32 source wire in 105 patients with restenotic and de novo lesions. It showed that beta-radiotherapy with the centered P-32 source is safe and highly effective in inhibiting restenosis at the target site after stenting or balloon angioplasty. However, edge narrowing and late thrombotic events must be addressed to maximize the clinical benefit of this treatment modality.

BETA CATH trial is the first and largest randomized, triple-masked, placebo-controlled trial designed with an intention to assess the safety and efficacy of the 30 mm Novoste™ Beta Cath™ (Sr/Y 90) source train in primary prophylaxis of restenosis in de novo lesions in conjunction with stand-alone PTCA or provisional stenting. The trial randomized 1450 patients. It essentially demonstrated a statistically significant reduction in all angiographic parameters in the "lesion" segment for the "PTCA" and "Stent" group treated with Sr-90. The positive significant effect of Sr-90 seen in the "lesion" segment, however, was lost in the "analysis" segment evaluation. The mechanism of restenosis in the Sr-90 arm appears to be limited to a zone outside the index lesion and may reflect zones of interventional injury in which there was low dose (geographic miss) or no dose of radiation. The primary endpoint, target vessel failure, was not shown to be significantly lower in the combined radiation arm compared with combined placebo arm. "Geographic miss" may have contributed to the negative results of Sr-90. The overall positive results in the "lesion" segment analysis and the strong trends in the improved clinical outcome of the PTCA/Sr-90 treatment group suggests a potential role for catheter-based Sr-90 in the prevention of restenosis in de novo lesions, provided that the increase in restenosis in the "analysis" segment can be solved. Perhaps, the use of a longer source train may help to address the issue.

Radioactive Stents

Clinical studies with more than 400 implants of P-32 Palmaz-Schatz (Cordis, Miami, FL) and Bx Velocity Radioactive P-32 stents (Cordis, Miami, FL) have demonstrated safety and feasibility of "stent-based" VBT. Late coronary thrombosis after stent-based irradiation is rare, but edge restenosis is a serious problem (candy-wrapper). The exact cause of the "candy-wrapper" phenomenon is largely unknown. Major research interest now focuses on the interaction of dosimetry at the dose fall-off zone at the edges. Stents with enhanced activities at the edges ("hot ends") to counteract the "low-dose" effect are being tested in Milan and Rotterdam. Minimizing barotraumas at the edges by using self-expanding radioisotope stents and better stent delivery platforms may help to overcome the edge restenosis issue. One may anticipate the resurrection of stent-based brachytherapy very soon.

Beta vs. Gamma

The tissue penetration of beta radiation is finite (<10 mm) and rapid deposit of energy in tissue is possible (2.5 to 4 minutes). Interventional cardiologists and cardiac catheterization laboratory personnel can stay in the room with the patient during treatment. The downside of the low penetration is that it may not be sufficient to treat large-diameter vessels. The beta energy may also be attenuated by calcium or the stent struts. On the contrary, gamma radiation is deeply penetrating. The dwelling time ranges from 12 to 35 minutes, depending on the dose rate of the system. A shielded room and auxiliary shielding around the patient are required.
Active Centering vs. Passive Centering

Centering catheter systems have been developed to improve dose homogeneity. However, centering the lumen does not necessarily imply centering the vessel wall due to the presence of eccentric plaque and angulated segments. The adventitia is a "moving target" relative to its central axis throughout the cardiac cycle. By allowing the delivery catheter to move "passively" inside the lumen may in fact attenuate the heterogeneity. True centering may require sophisticated differential shielding guided by intravascular ultrasound. The Brigade™ Brachytherapy system (Endosonics, CA) is an IVUS-guided directional radiation system, which is being tested by the Cleveland Clinic Foundation to serve this purpose. Radioactive liquid or gas-filled balloons may provide a more uniform dose to the vessel wall. However, the disadvantage is the potential risk of leakage and ischemia due to complete vessel occlusion during treatment. Liquid Rhenium-188 appears to be a safer alternative to other liquid sources because Rh-188 is rapidly excreted via the kidneys in case of leakage, whereas liquid P-32 and Sr-90 have very high affinity for bone, resulting in bone marrow toxicity. Radiance RDX™ (Radiance Medical System Inc., Irvine, CA) is a solid source P-32 balloon catheter which is being tested under clinical trials. Like liquid-filled balloon, it has the advantage of dose homogeneity. However, "shelf-life" is a practical issue that needs to be addressed. After all, there is as yet no data suggesting any delivery system is superior to the other.

The "Dark side" of VBT

Among the complications associated with vascular brachytherapy is a new phenomenon of late coronary thrombosis (>30 days), which was probably caused by delay in re-endothelialization. Meta-analysis of 6 vascular brachytherapy trials revealed a late thrombosis rate of 9.1% in the radiated group, compared with 1.2% in the placebo group. (p<0.0001)48-51 Multivariate analysis determined that new stenting was the main predictor of late thrombosis. Two prospective studies, SCRIPPS-III and WRIST-Plus, have provided data for use in assessing the effectiveness of extended antiplatelet medication for prophylaxis against late thrombosis when brachytherapy is used in the treatment of ISR. In the SCRIPPS-III registry, thrombosis-free survival was 99% at 210 days at the time of the review of the Checkmate™ device for pre-marketing approval. Notably, patients in the SCRIPPS-III registry who had new stents received antiplatelet therapy for 12 months. WRIST-Plus demonstrated that 6 months of clopidogrel and aspirin therapy after VBT and minimizing stent use during intervention for patients with ISR resulted in a reduction of late thrombosis rates to background levels that were similar to the placebo group.52 The late total occlusion of START and INHIBIT were 0.5% and 1.8% respectively.38,39 The FDA, therefore, requires that the labeling of the gamma-radiation device explicitly advise avoidance of the placement of new stents and maintenance of antiplatelet therapy for a minimum of 6 months after brachytherapy and for 1 year if a new stent was implanted. A warning to avoid the placement of new stents was also required in the labeling of the Beta-Cath™.

"Candy-wrapper" phenomenon was observed in patients treated with radioactive P-32 stents and catheter-based radiation brachytherapy.46,47 It has been postulated that the edge effect is probably due to interventional injury at the edges which did not receive the prescribed dose of radiation (geographic miss). Low dose radiation may, in fact, stimulate VSMC proliferation. Several studies have shown that geographic miss is associated with higher target vessel failure rates after brachytherapy.42,53

IVUS follow-up of patients who underwent brachytherapy revealed a phenomenon of late stent mal-apposition, which was probably caused by vessel expansion (positive remodeling).54,55 Another IVUS finding after VBT was the "black hole" behind the stent, which may cause late lumen loss. In fact, it corresponded to the collagen-deficient matrix and fibrin accumulation after brachytherapy seen in the animal model and autopsy. The clinical significance of these IVUS findings is still under investigation.

Aneurysmal dilation is associated with high doses of radiation. Indeed, in the initial human intracoronary radiation trials, 4 aneurysms have been reported. In retrospective calculation, these patients received doses as high as 92 Gy at the luminal surface of the vessel wall. Nowadays, aneurysm has not been associated with contemporary "therapeutic" dosimetry in clinical brachytherapy trials and registry.
The Hong Kong Experience with VBT

The first gamma radiation brachytherapy program in Hong Kong was started in May 2000 in Pamela Youde Nethersole Eastern Hospital. 16 patients with ISR were successfully treated using the Checkmate™ Iridium-192 system with 100% procedural success rate. The mean dwell time was 19.4±2.4 minutes. There was no in-hospital MACE.56

The first beta-radiation brachytherapy program was started in July 2000 in Grantham Hospital. 57 52 patients underwent PCI followed by β-radiation brachytherapy using the Beta-Cath™ 40 mm Sr/Y-90 source train. The mean age was 68.5±6.8 (45-86) years. 36 ISR lesions were treated under a surveillance registry protocol. 23 patients with de novo ostial LAD lesions were enrolled in a pilot study protocol to evaluate the safety and efficacy of the 40 mm source train in reducing restenosis in high-risk de novo lesion subsets. Vessels treated were 40 LAD (1 with left main involvement), 7 left circumflex, 7 right coronary arteries, 1 ramus intermedius and 1 saphenous vein graft. Excimer Laser Coronary Angioplasty was used in 4 cases, cutting balloon in 8, rotational atherectomy in 2, Angioguard™ distal protection filter-wire in 1 and new stents in 24 patients. Device success was 98% and procedural success was 100%. Active dose of 18.4 to 25.3 Gy was prescribed according to the vessel size. Manual pullback technique was used in 12 cases for lesions >26 mm. Off-line Quantitative Coronary Analysis was performed using CAAS II QCA program. Mean pre-procedure reference diameter was 3.24±0.23 mm. Minimal Luminal Diameter was increased from 0.21±0.41 mm to 3.02±0.63 mm. Mean diameter stenosis was reduced from 89.1% to a final residual stenosis of 5.8%. Mean injury and radiated length was 24.4±8.3 mm and 47.2±15.2 mm, respectively. Geographic miss was noted in 4 patients. There was no in-hospital MACE. All patients received aspirin for life and clopidogrel for 6 to 12 months. Mean follow up period was 30.4 (1-48) weeks. There was 1 sudden arrhythmic death 21 days after brachytherapy. The patient was enrolled in the compassionate use protocol because of low ejection fraction of <20%. No clinical stent thrombosis was recorded. 6-months angiographic follow-up has been completed in 22 patients (20 ISR and 6 de novo ostial LAD lesions; 5 patients received pullback radiation). There was 1 silent late occlusion and no aneurysm.

Binary restenosis was reported in 1 patient, who underwent repeated PCI. Median late lumen loss and late loss index was 0.03 mm and 3.7%, respectively.

Future Directions

Undeniably, vascular brachytherapy has emerged as a viable treatment option for restenosis prevention. The explosion of research in this field is overwhelming. Notwithstanding, VBT is far from perfect. Investigators soon realized the limitations and dark side of VBT. As with any cutting-edge technology, unexpected complications may dampen the initial unbridled expectations and result in skepticism. Nevertheless, time, experience and painstaking data analysis has substantiated the niche role of VBT in reducing instent restenosis. Prolonged clopidogrel therapy has apparently relieved the tension on the late thrombosis issue. However, more work still needs to be done on the long-term effects of VBT as the adverse sequel of radiation may take years to ensue. It is also high time to evaluate the cost-effectiveness of various brachytherapy systems comprehensively as more and more centers are establishing their own VBT programs around the world. The promising preliminary clinical data from drug-eluted stents have aroused the next tidal wave in interventional cardiology. While some believe that it is the death knell of brachytherapy, others, the pathologists in particular, worry that it may be just the beginning of another never-ending story. Nonetheless, novel polymer technology has provided an excellent platform for local drug delivery. Various drugs, like sirolimus, paclitaxol, actinomycin D, etc. are now being tested under various clinical trials. However, drug-eluted stents are not faultless. SCORE trial, which randomized patients to taxol-coated Quanum stents and bare stents, was prematurely terminated because of increased MACE in the "taxol" arm.58 Presumably, whatever attempts to inhibit the healing process will delay re-endothelialization and enhance the propensity for late thrombosis. From the pathophysiological perspective, anti-proliferative drugs inhibit neointimal proliferation in a pretty much similar manner as brachytherapy. Taxol has a very narrow therapeutic window. The "toxic" dose can cause excessive fibrin accumulation and medial necrosis. Dosimetry and pharmacokinetics are thus important considerations. In some animal models, taxol-
coated stents merely delay the healing response. The restenosis process catches up rapidly after the drug-release is over. Nevertheless, randomized, placebo-controlled clinical trials are underway to unravel the myth.

The quest for new technology in restenosis prevention has never ceased. Novel advances, like sonotherapy, photodynamic therapy, cryotherapy, miniaturesoft X-rays, biodegradable stents, etc., are in different phases of development and clinical trials. Although there are a lot of contenders in the arena, vascular brachytherapy is by far the only one that has accumulated sufficient clinical evidence to substantiate its capability in restenosis prevention.

References
CURRENT STATUS OF INTRACORONARY RADIATION BRACHYTHERAPY

44. Fischell TA. Radioactive stents [In Process Citation]. Semin Interv Cardiol 1998;3:51-6.