The Bright and the Dark Sides of Brachytherapy

Mechanisms of Stenosis Reduction and Findings of Intracoronary β-Radiation Therapy Revealed by IVUS-3D and QCA

The Bright and the Dark Sides of Brachytherapy: Mechanisms of Stenosis Reduction and Findings of Intracoronary β-Radiation Therapy Revealed by IVUS-3D and QCA

De zonzijde en de schaduwzijde van brachytherapie: het mechanisme van restenose-reduktie en bevindingen bij IVUS-3D en QCA

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I-B: Mechanistic Interpretation of Brachytherapy

Introduction

Since the first percutaneous coronary intervention, 24 years ago, the field of interventional cardiology has continued to grow rapidly. Although PTCA has demonstrated superiority to medical therapy in alleviating angina, restenosis and acute closure of the treated vessel remained major limitations. Stent has improved both problems by preventing residual dissection, elastic recoil and negative remodeling. However, the occurrence of restenosis after stenting remains unresolved. Furthermore, in-stent restenosis has become a new enemy in the field of interventional cardiology, since the conventional treatment of in-stent restenosis is rather disappointing with high restenosis rates (around 30 – 70%). Therefore, the holy grail to overcome this immense enemy went unabated.
Intracoronary brachytherapy is a powerful therapy to prevent restenosis after percutaneous transluminal coronary intervention. The purpose of this thesis is to explore the mechanism of action of intracoronary radiation and the problems related to this procedure. For this purpose, three-dimensional intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) were applied as investigational tools.
This thesis consists of 2 parts; the first part deals with the positive aspect of intracoronary brachytherapy which explains its increasing application (Chapter 2) and its mechanistic interpretation (Chapters 3-7). The second part reports on the dark sides of intracoronary brachytherapy (Chapters 8-12).
The first chapter presents an overview of intracoronary brachytherapy. The feasibility of its routine use is discussed in the second chapter.
From chapter 3 to chapter 7, the morphological changes within the irradiated vessel wall segments and its edges were studied by means of ECG-gated volumetric IVUS and QCA. In chapter 3, volumes of the vessel lumen and the total vessel were compared between segments that had radiation plus balloon angioplasty, radiation plus stenting, control balloon angioplasty, and control stenting. In chapter 4, the non-injured edge of irradiated segments was investigated using ECG-gated volumetric IVUS analysis. The data presented in Chapter 5 show the relationship between plaque growth and tensile stress as well as actual dose delivered to the adventitia. In Chapter 6 and 7, the new methodology and the usefulness of QCA in the setting of intracoronary brachytherapy, which has a potential to increase the lumen and vessel size, are described. In chapter 7, both the sensitivity and specificity of positive remodeling assessed by QCA and compared to the gold standard: IVUS analysis are reported.

In Chapter 8 to 12, the deleterious effects of coronary brachytherapy were investigated; edge effect, late thrombotic occlusion, delayed restenosis, black hole, and late stent malapposition. Those problems need to be solved in order to propose intracoronary brachytherapy as a treatment modality.

Part I-A

The Rise of Brachytherapy

Widely use of Brachytherapy

Chapter 1

Coronary Brachytherapy

(book chapter for Euro CVS)

Coronary Brachytherapy

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Introduction

Restenosis remains the major limitation of percutaneous, catheter-based interventional therapy. The endovascular application of radioactivity represents a relatively new and promising tool to overcome this limitation. This chapter summarizes the clinical experience and gives an overview of the current practice.

Definition

Brachytherapy is derived from the Greek "βραχυς" (brachy) meaning short and "θεροπεια" (therapy) meaning treatment to describe the application of radioactivity by a sealed source at a very short distance to the target tissue, e.g. by intracavitary or interstitial source placement. Recently, the term vascular brachytherapy has been introduced to describe endovascular radiation therapy.

Rationale

Radiotherapy has been proven successful in the treatment of hypertrophic scars, keloids, heterotopic bone formation, ophthalmic pterygia years1-3 and solid malignancies4. In non-malignant diseases, radiation inhibits efficiently fibroblastic activity, without influencing the normal healing process, and without causing significant morbidity during long term follow-up of up to 20 years.

Brachytherapy has the physical benefit that very high doses of radiation can be delivered directly or almost directly to the target.

First human experiences

The first clinical trial was initiated in 1990 in patients with in-stent restenosis of femoropopliteal arteries using gamma (Ir-192) radiotherapy5. Human coronary arteries were treated for the first time by Condado et al. in 1995: De novo lesions where treated by balloon angioplasty followed by gamma-radiation (Ir-192). No restenosis was observed after 6months6. Also in 1997, Teirstein demonstrated the effectiveness of gamma therapy for the treatment of in-stent restenosis7, whilst Verin reported the feasibility of beta sources after balloon angioplasty8. Today, a variety of controlled clinical trials, which are summarized below, provide information for both, gamma and beta-radiation treatment.

Basic radiation physics

Radioactivity

Radioactivity is the spontaneous process in which an unstable nucleus, which has either too many or too few neutrons, turns to a stable state (ground state) whereby superfluous energy is released.

The release of energy is called radiation, which can be electromagnetic waves, like gamma, or particle rays, like alpha, beta or neutron rays. This process is often called the "disintegration" of an atom. Mathematically the activity can be expressed by the number of disintegrations dN within a time interval dt (A=ó dN/dt). In the international system (SI) of units this quotient is called the becquerel (Bq).

DECAY

For most atoms the activity is proportional to the number of atoms (A=λN). The proportionality constant is called the decay constant. This leads to the decay law, At=A0exp(ó λt), and λ=ln2/T1/2 whereby T1/2 is called the "physical half-life time", being the time that the original activity of a nuclide has been reduced with a factor two. The physical half-life time is characteristic for nuclids (distinct nuclear species) and isotopes (various forms of an element).

BIOLOGICAL HALF-LIFE

Biological half-life is the time needed by the body to eliminate one-half of an administered amount of any substance by regular process of elimination. This time is approximately the same for both, stable and unstable isotopes of the same element.

ABSORPTION - RADIATION DOSE

The released energy during transformation of an unstable atom into a stable atom is absorbed in tissue. The quantity of absorbed energy in a tissue is called the "dose" with the SI unit Gray (Gy=J/kg). The dose is strongly dependent of the type of radiation (activity and decay) and the time span, also called "dwell time".

RADIATION DOSE RATE

Dose rate is the dose of radiation per time (delivered or received). The dose rate delivered by a source depends on the activity of the source and the radionuclide it contains. Currently, all removable vascular brachytherapy sources deliver energy at high dose rate, while radioactive stents deliver energy at low dose rates.

EQUIVALENT DOSE

The biological effects of the absorpted radiation are dependent on the type of radiation and the type of tissue. This is expressed by weighting factors for the type of radiation and for the specific organ or tissue. After correction the dose is called the equivalent dose. In the field of radiation protection measurements it is this dose to be used.

ISODOSE

Description of a locus where the absorbed dose is the same at any point.

CURRENTLY USED ISOTOPES

The most important physical properties of currently used isotopes in vascular brachytherapy are listed below.

Isotope	Emission	Max. Energy	Av. Energy	Half-life
^{192}Ir	gamma	612 keV	375 keV	74 days
^{90}Sr/^{90}Y	beta	2270 keV	970 keV	28 years
^{32}P	beta	1710 keV	690 keV	14 days

These isotopes show important physical differences. Basically, gamma radiation consists of photons, beta radiation of electrons.

GAMMA RADIATION

Gamma rays are photons originating from the center of the nucleus, which take the form of electromagnetic radiation. A heavy unstable nucleus will emit an alpha (heavyweight charged particle, which travels only very short distances within tissues) or beta particle followed by gamma radiation. Gamma rays may have either 1 or 2 discrete energy values or a broad spectrum of many energy values. They penetrate deeply within tissues.

X-RAY RADIATION

X-rays are comparable to gamma radiation. Their physical characteristics are similar, however, their origin is different. While the photonts of gamma radiation originate from the nucleus, the photons of x-rays originate from the electron orbit.

BETA RADIATION

Beta particles are lightweight high-energy electrons, with either positive or negative charge. When beta particles, which travel only finite distances within tissues, are slowed down by nuclei interactions, they give rise to high penetration X-rays, called Bremsstrahlung.

The interaction of photons with other material is lower than the interactions with electrons. That means, the energy transfer to other material is less intensive for gamma than for beta radiation. In the setting of brachytherapy, this has two major consequences.

a) Dwell time: to obtain a defined dose in a tissue at a certain distance from a source, gamma sources require much higher activities or much longer dwell times in comparison to beta sources.

b) Radiation exposure: the exposure to the staff inside and -because of deep tissue penetration- outside the catheterization laboratory is much higher during treatment with gamma radiation than beta radiation. In consequence, staff should leave the catheterization laboratory during radiation treatment and additional shielding facilities have to be implemented.

Mechanisms of action

Cell biological effects

Absorbed radiation can cause damage in a tissue either directly by ionization or indirectly by interacting with other molecules to produce free radicals, which will subsequently damage the critical target. Approximately 80% of the radiation damage is caused by these free radicals. The most critical target is DNA9, in consequence, early and late toxic effects in normal tissue are mainly caused by cell death.

These biological effects are independent of the radiation type (gamma, beta or X-rays) whereas total radiation dose and dose rate are of major importance, since damage caused by radiation can be repaired between fractionated doses or during low dose rate exposure10. Furthermore, there seems also to be inverse dose rate effects in demonstrated in human cells most probably by blocking cells in the mitosis (G2) phase of the cell cycle by at low dose rate (approx. 6mGy/min), which is known to be more radiosensitive, thereby causing more cell death.

Experimental data

In injured vascular tissue, radiation doses of 12-20 Gy appear to be efficacious in inhibiting neointimal formation12-14. The local mechanisms of action are complex, dose dependent and poorly understood. Possible high dose radiation effects include selective inactivation of smooth muscle cells and myofibroblasts15, or complete elimination of their proliferative capacity at doses >20 Gy. Application of lower dose could mean, that restenosis would only be delayed for the period of time necessary for the population of smooth muscle cells to regenerate. Furthermore, low-dose radiation (4-8 Gy) even promotes cellular growth16 possibly by growth factor release17.

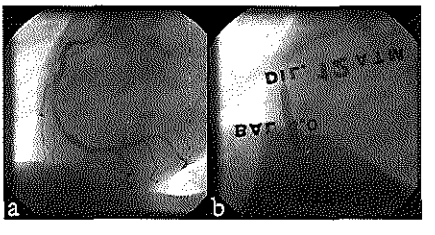
Clinical data

Balloon angioplasty followed by irradiation predominantly shows an increase in minimal lumen diameter at the treated segment at follow-up6. This is in contrast to standard balloon angioplasty, where late lumen loss caused by neointimal growth and vessel shrinkage is the usual response18,19. Irradiation inhibits neointimal growth20, may prevent shrinkage after balloon angioplasty21 and even promote positive remodeling at the treated segments22.

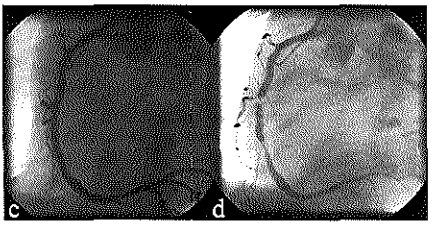
Candy wrapper effect

In contrast, edge segments show an increase in plaque volume without adaptive remodeling23,20,24, causing the "edge effect" or "candy wrapper effect", first described by Albiero et al.25 (Figure1).

Figure 1.The "candy wrapper effect" induced by implantation of a radioactive stent.



a) pre-procedural angiogram, b) direct stenting with an ACS radioactive stent (4.0/20mm at 12 atm)

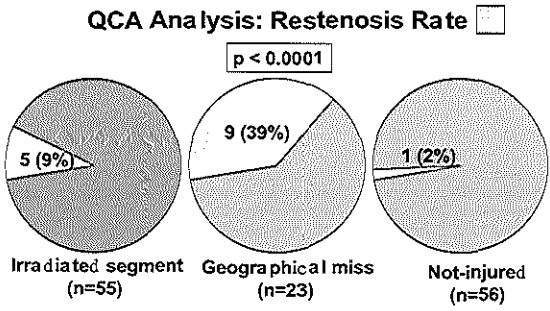


c) final angiogram d) angiogram at 6 months follow-up, showing narrowing at the proximal and distal edge of the stent.

Geographic Miss

In concordance with known cell biological effects and animal data, low dose radiation at the extremities of the source and angioplasty induced vessel injury, referred as "geographic miss" seems to play a key role in edge restenosis and treatment failure for (beta) brachytherapy26,27 (Figure2).

Figure 2.



Association between geographic miss and restenosis rate

QCA = quanitative coronary analysis, IRS = irradiated segment, not injured = not injured edge segment.

Contemporary application modalities and devices

Vascular brachytherapy can be performed by catheter-based systems, radiation balloons (both high dose rate) or radioactive stents (low dose rate). In the U.S two systems, the Novoste Beta-Cath and the Cordis Checkmate have the FDA approval up to now. In Europe, the following systems are actually in clinical use.

THE CHECKMATE SYSTEM (CORDIS):

Radiation type: Gamma (192Ir)

Delivery catheter: Multilumen, non-centering catheter (blind lumen for source train), compatible with 7F guiding catheter and 0.014 inch guide wire.

Dummy ribbon: 22 non-radioactive seeds in a nylon sheath. X-ray markers at each end.

Source: 192Ir seed train. Treatment length 23mm (6 seeds), 39mm (10 seeds) and 55mm (14 seeds). Non-radioactive, X-ray markers at each end.

Source delivery unit: Hand cranked afterloader for mechanically advancing and withdrawing of the source ribbon.

THE BETA-CATH SYSTEM (NOVOSTE):

Radiation type: Beta (90Sr/90Y)

Delivery catheter: 5F Multilumen, non-centering catheter (two closed lumen for radiation source train and fluid return lumen; one open lumen for guide wire) compatible with 8F guiding catheter and 0.014 inch guide wire. X-ray markers at each end.

Dummy ribbon: Passive source trains with X-ray markers at each end.

Source: 90Sr/90Y seed train. Treatment length 30mm (12seeds), 40mm (16 seeds) and 60mm (24seeds). Non-radioactive, X-ray markers at each end.

Source delivery unit: Hand held afterloader for hydraulic advancing and withdrawing of the source ribbon (sterile water).

THE GALILEO SYSTEM (GUIDANT)

Radiation type: Beta (32P)

Delivery catheter: Multilumen, centering balloon-catheter (spiral design) compatible with 7F guiding catheters and 0.014 inch guide wire. Balloon length 32mm and 52mm, balloon diameter 2.5mm, 3.0mm and 3.5mm. X-ray markers at the extremities of the balloon.

Dummy ribbon: ñññññññ-

Source: 32P wire (0.018inch). Source length is 20mm, sealed at the wire tip. Non-radioactive X-ray markers are placed to bracket 80% therapeutic dose range of the wire proximally and distally to the source.

Source delivery unit: High dose rate afterloader with computer controlled advancing and withdrawing of the source wire. Delivery system

calculates the treatment time automatically and performed automated pullback of the source (stepping procedure).

The first and principal step in deciding on a brachytherapy system is the question of radiation type. The clinically and practically most relevant advantages and disadvantages are as follows:

Gamma radiation

Pros:

Ï Effective in randomized, double blind, placebo-controlled trials

Ï Deep tissue penetration (ideal for large vessel diameters)

Ï No attenuation by stent struts (ideal for instent restenosis)

Cons:

ó Extensive shielding required (25mm lead)

ó High radiation exposure for patient and staff

ó Staff has to leave catheterization laboratory

- Long dwell times (8-20 min)

Beta radiation

Pros:

Ï Simple shielding by means of thick plastics

Ï Short dwell times (3-10 min)

Ï Radiation exposure to the patient only local

Ï Radiation exposure to staff is negligible

Ï Staff can remain in the catheterization laboratory

Cons:

ó Lack of data concerning its efficacy except in-stent restenosis

ó Probable not able to treat vessels with diameters >4 mm (with existing devices)

ó Inhomogenicity of the dose (evtl. centering device required)

ó Partially shielded by stents and calcified plaques

ó Dose distribution calculations of beta emitters are more complicated.

Radiation protection and safety considerations

Radioactive material cannot be turned off. Therefore, secure control of the radioactive inventory and surveillance of staff and patients is of special concern.

Regulatory considerations

For transportation, storage and handling of nuclear sources, European countries require various licenses according to individual nuclear laws.

In general, the institute or hospital needs a license for using radioactive material. Within the institute or hospital a local permission has to be

obtained which is mostly linked to specific room conditions and expertise of the personnel. Mandatory key personnel includes a radiation oncologist, a medical physicist, a radiation safety officer and a cardiologist. Clinical responsibility lies with the radiation oncologist, though he may delegate practical aspects to others.

Practical safety considerations

In Europe, standards for the protection of patients, health workers and the public against exposure to radiation have been specified in two directives (96/29/EURATOM: 97/3/EURATOM) and are now being incorporated into national laws. Radiation protection is determined by two principles: exposure must be justified by showing that it confers more benefit than detriment and exposure should be as low as reasonable achievable.

MONITORING

Individual personnel dosimeter badges allowing for effective dose equivalent reading are mandatory in controlled areas like catheterization laboratories. Radioactivity can be further assessed by two basic instruments, the portable Geiger-M¸ller (GM) counter and the ionization chamber survey meter.

SOURCE

Every source must be inspected on receipt, which involves visual inspection in the shielding, calibration to verify the exact level of activity and, in line-sources, checking the number and activity of sources.

STORAGE

Sources must be stored securely and held under lock and key. The time necessary to transfer the source in a special delivery device (pig) to the laboratory must be taken into account by treatment protocols. The storing facilities must provide sufficient shielding not only for the gamma (192Ir) sources, but also for the beta (90Sr/90Y and 32P) sources, which produce significant Bremstrahlung. 32P has a half-life of 14 days only. In consequence, 32P sources have to be exchanged every two weeks. 90Sr/90Y sources require a yearly check especially for the mechanical condition of the source.

CATHETERIZATION LABORATORY DESIGN AND EQUIPMENT

Actual shielding requirements are catheterization laboratory specific depending on size and configuration of the procedure room and the adjacent rooms. Principially, when working with gamma radiation, special shielding (minimum thickness 25mm lead) is required in the procedure room to block the gamma rays (e.g. mobile shields of approx. 200kg positioned close to the patient). The control room must be protected by a mobile lead shield. Outside the laboratory, the level of exposure must be estimated and regularly monitored in adjacent rooms.

Beta radiation requires no specific shielding of the catheterization laboratory or adjacent rooms.

PATIENT SAFETY

Principal risks related to intracoronary radiation include

- damage to the artery wall with consecutive perforation and/or aneurysm formation. This risks seems to be dose related (>30Gy) and low6,28-31.

- accelerated coronary artery disease as known side-effect of high dose radiation (>35 Gy) for the treatment of neoplasms32-34. Intermediate doses (30-40 Gy) have shown a low risk of cardiac disease during long term follow-up35.

- radiation-induced carcinogenesis. This risk appears to be low at least in beta radiation as the dose beyond the immediate target lesion is low and the exposed tissues (e.g., arteries, veins, cardiac muscle, and pericardium) have a low spontaneous carcinogenicity rate.

Technical risk related to intracoronary radiation

The main technical risks related to intracoronary radiation is the failure to smoothly deploy and retrieve the source. Therefore, proper source passage into the target coronary artery should be routinely tested by deploying and retrieving a dummy source. A dummy source allows also for control of the treatment position within the coronary artery and repositioning of the delivery catheter if necessary.

STAFF SAFETY

Every source is brought into the catheterization laboratory in a shielding device (pig). The shielding device can be a source of radiation. The operatorís hand dose can be reduced by not touching the shielding device. During delivery into the coronary artery and retrieval, the source is unshielded for a few seconds. Again, the operatorís dose is reduced by not touching the treatment catheter and keeping distance. Direct finger contact with a high dose rate source is hazardous. During treatment with gamma radiation, all personnel with exception of the radiation oncologist must leave the catheterization laboratory in order to limit their exposure to radiation.

Procedure performance

Intravascular radiation treatment requires a substantial commitment and collaboration between the interventional cardiologist and the radiation oncologist. Prior to every brachytherapy procedure, the radiation oncologist and the medical physicist have to be informed. The radiation oncologist must be able to review the patientís anamnesis and physical condition for proper treatment planning, the medical physicist guarantees secure source transportation.

Patient selection

INDICATIONS

Up to date, there exists no established indication for brachytherapy. Potential indications include all circumstances with elevated risk for restenosis after conventional catheter based intervention such as long lesions, sapheneous vein grafts, small coronary arteries, in-stent restenosis, multivessel disease, diabetic patients and renal insufficiency patients. In the US, FDA approval is limited to the treatment of in-stent restenosis.

CONTRAINDICATIONS

Contraindications are previous radiotherapy of the chest, previous intracoronary brachytherapy, pregnancy, genetic radiation sensitivity disorders (e.g. ataxia-telangiectasia).

Patient preparation - medication

Pre-procedural treatment requires no particular medication for brachytherapy other than antiplatelet regimen for routine angioplasty procedures: Aspirin (75mg-300mg) and ticlopidine or clopidogrel must be started at least 24h before the procedure, whereby we prescribe a loading dose of 750mg, followed by 250mg twice a day for ticlopidine and a loading dose of 300mg, followed by 75mg daily for clopidogrel. Beta-blockers, calcium antagonist and oral nitrates should be administered as usually prescribed.

At the begin of the procedure, we routinely administer neuroleptics and analgesics. Repeat bolus is given during the procedure, if needed. This is especially helpful when using an afterloading technique, as it prolongs procedural time and creates significant ischemia during radiation in the majority of the patients. Furthermore, we administer 325mg aspirin intravenously and 10 000 IU heparin immediately after arterial sheath placement. Activated clotting time (ACT) is checked every 30 minutes after the first bolus injection in order to maintain ACT > 300 sec. Additional heparin is given if necessary.

During the procedure, GP IIbIIIa receptor blockers are given deliberately in patients with unstable angina, periprocedural intracoronary thrombus formation or dissection.

Equipment set-up and special arrangements of the operating room

For the angioplasty procedure, a standard angioplasty set and eventually additional ablative devices (e.g. atherectomy catheter) is needed.

For brachytherapy, the catheterization laboratory must have appropriate shielding as described in section 5.2. The radiation oncologist prepares the brachytherapy device (e.g check for mechanical integrity, flushing of the system, dummy source, etc). We recommend for this purpose an extra sterile table and light. A bail-out box must be in the procedure room, typically consisting of an assortment of long-handled instruments for grasping a source and of a shielded container (lead for gamma radiation, plastic for beta-radiation source) to safely place the source. Radiation detectors to survey the environment during the procedure and contamination monitors for source leakage are needed. At least two timers must be available to allow for correct dwell time and to minimize treatment errors.

During a gamma radiation procedure, additional sterile gowns and gloves should be open on a table in the treatment room for cases of emergency when staff members need to rapidly approach the patient.

Access method

We prefer the standard femoral approach for optimal guide support using a 8F sheath and guiding catheter.

Angiography

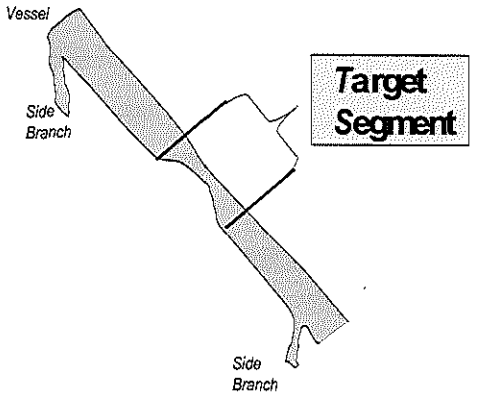
TERMINOLOGY

Brachytherapy as new treatment with complex mechanisms of action urges detailed angiographic assessment and necessitates the introduction of a new terminology.

ï Target segment (Figure 3)

The target segment is defined by the proximal and distal margin of the obstructed segment.

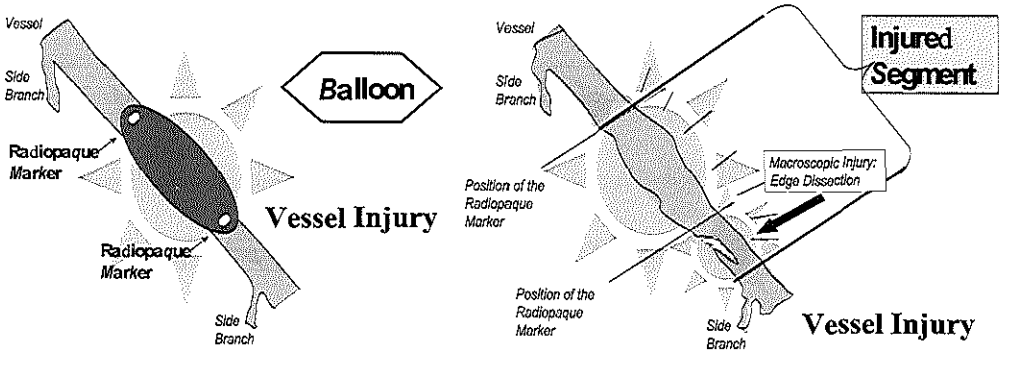
Figure 3.



ï Injured segment (Figure 4)

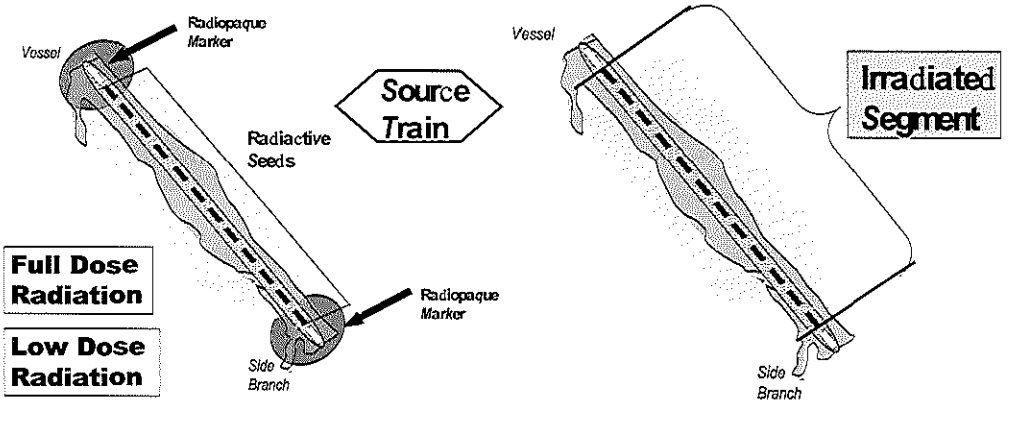
The macroscopic injured segment is defined as the segment encompassed by the most proximal and most distal position of the angioplasty device (e.g. rotablator burr) or marker of the angioplasty balloon and all visible vessel injury as assessed by flouroscopy.

Figure 4.



ï Irradiated segment (Figure 5)

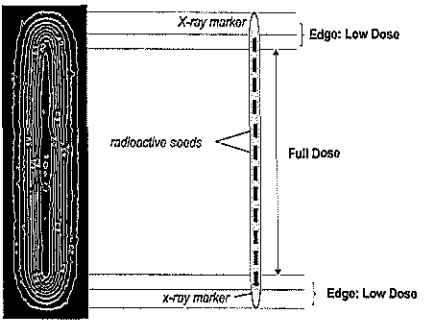
Figure 5.



The irradiated segment is defined as the segment encompassed by the inner edge of the radiopaque markers of the source train or the length of the radioactive stent.

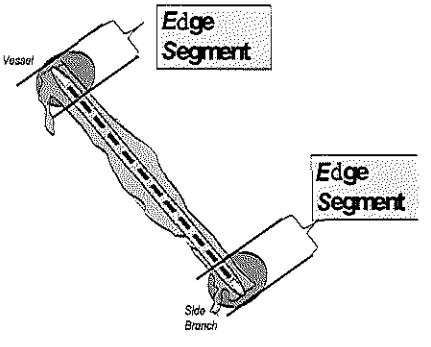
It is of note, that the effective irradiated segment receiving full prescribed therapeutic radiation dose (>90% isodose rate) is slighty shorter as a result of the dose fall-off caused by the limited size of the source train. The exact delineation of the effective irradiated segment is complicated, as is requires the knowledge of the individual dose-profiles for each isotope and source design (Figure 6).

Figure 6.



ï Edge segments (Figure 7)

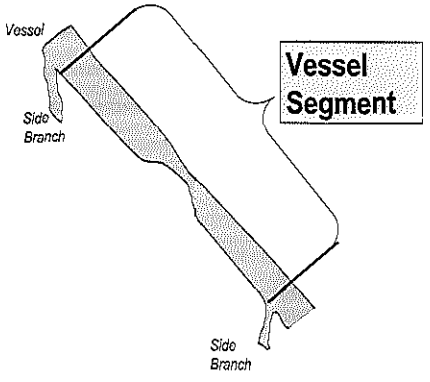
Figure 7.



Edge segments are the vessel segments at the extremities of the radiation source (catheter-based source, radioactive stent or balloon), which do not receive full therapeutic radiation dose. The lengths of the edge segments is dependent on the isodose profile of the individual source.

ï Vessel segment (Figure 8)

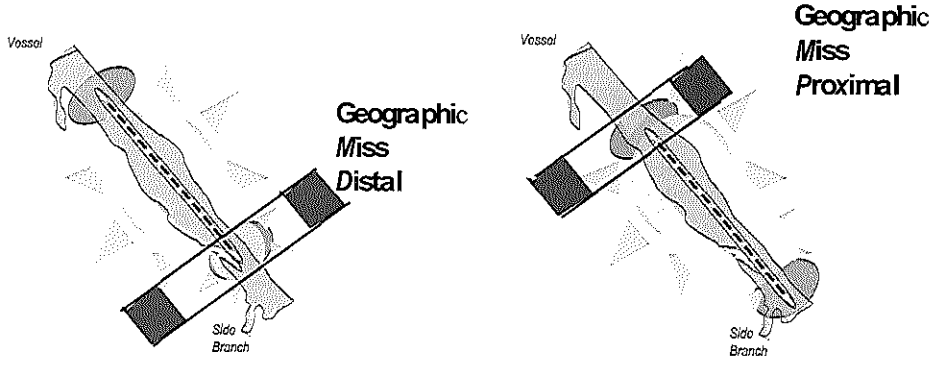
Figure 8.



The vessel segment is the coronary segment bordered by angiographically visible sidebranches which encompass the original lesion, all angioplasty devices and the radiation source.

ï Geographic miss segment (Figure 9)

Figure 9.

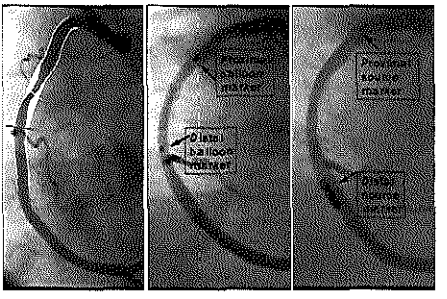


In coronary brachytherapy, it is defined as a mismatch between injured and irradiated segment: Geographical miss is present when the entire length of the injured segment is not completely covered by the irradiated segment.

GENERAL REQUIREMENTS

Angiography should be done in biplane views. At the start of the procedure, two projections are selected with more than 30degrees difference in rotation and avoiding foreshortening and side branch overlapping. The entire procedure should be filmed in identical projections. The meticulous documentation of all angioplasty devices and the radiation source in place with contrast medium, using the same projections, is essential (Figure 10).

Figure 10.



Angiographic documentation of a brachytherapy procedure. All angiograms should be performed in the same projection. Angioplasty devices (here: deflated balloon) and source should be filmed with contrast to allow for precise anatomical orientation.

Inadequate angiographic documentation, hampering the identification of the irradiated and the injured segment is seen in up to 50% of the cases enrolled in brachytherapy trials.

PRIMARY ANGIOGRAPHY

Primary angiography identifies the culprit lesion, the "target segment" and the "vessel segment". Basic considerations are:

- vessel size (dose prescription? radioactive stent selection)
- lesion accessibility for the source (dimensions, stiffness?)
- lesion position (ostial lesions virtually have geographic miss as source positioning with a proximal safety margin is not possible)
- strategy of angioplasty prior to radiation
- lesion length (source long enough to cover complete injured segment?)
- side branches (in bifurcation lesions, only 1 side branch can receive radiation)

Primary angiography also serves for decision on the "best projection" to document the complete procedure. Eventually necessary additional shielding (gamma radiation) has to be considered. The image intensifier has to be positioned in such way, that the lead shielding can be placed closely to the patient.

Angioplasty

Prior angioplasty might consist in debulking (directional or rotational atherectomy, laser), stent implantation or "simple" balloon inflation and is performed in conventional technique. Any instrumentation has to be filmed at the site of treatment surrounded by contrast medium in identical projections! It is important, that angioplasty is not stopped before reaching a satisfactory result. Every instrumentation after radiation therapy carries inevitably the risk of geographic miss.

Dose prescription and source selection

The treated coronary artery is usually 2-5 cm of length, with a diameter of 3-5 mm and a vessel wall thickness of 0.5-3 mm. The radiation dose given to the vessel wall should probably target the media as well as the adventitia delivered at 0.5-5mm from the source. Dose prescription and source selection are performed in close collaboration with the radiation oncologist. Dose is prescribed in relation to the long axis of the source (e.g. at 2mm).

CATHETER BASED AFTERLOADING SYSTEMS

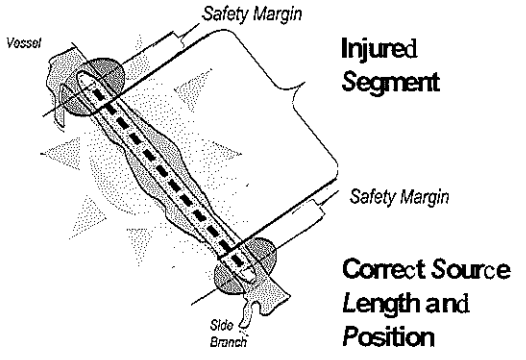
Given the radioactivity and dose rate of the selected source, dwell time is calculated in dependency of the vessel size.

The length of the source should be selected in that way, that

- the vessel segment, which has been "touched" by any angioplasty device and
- the vessel segment which shows macroscopic injury is completely covered
- there is sufficient safety margin at the proximal and distal end of the source to guarantee full dose radiation of the treated segment.

In practice, we select the length of a source train with a "safety margin" of 1 seed to be outside the injured segment at each end (Beta-Cath system, Checkmate system) (Figure11).

Figure 11.



Correct selection of the source length and positioning. The source should be longer than the injured segment to guarantee full dose radiation. The source has to be positioned with a proximal and distal safety margin. The length of the safety margin (here: one seed) is dependent of the source design and isotope.

RADIOACTIVE STENTS

The dose is given by the radioactivity and dose rate of the stent. Stent diameter is conventionally selected according to the vessel diameter (stent to reference vessel diameter ratio1.1). The radioactive stent has to be longer than the lesion accounting for the dose-fall of at the extremities of the stent.

Radiation treatment

The radiation oncologist prepares the brachytherapy device. Meanwhile it might be helpful for the operator to review the angiograms. This allows for a precise image of the "injured segment" relative to landmarks such as side-branches. If necessary (gamma radiation), lead shielding devices have to be installed.

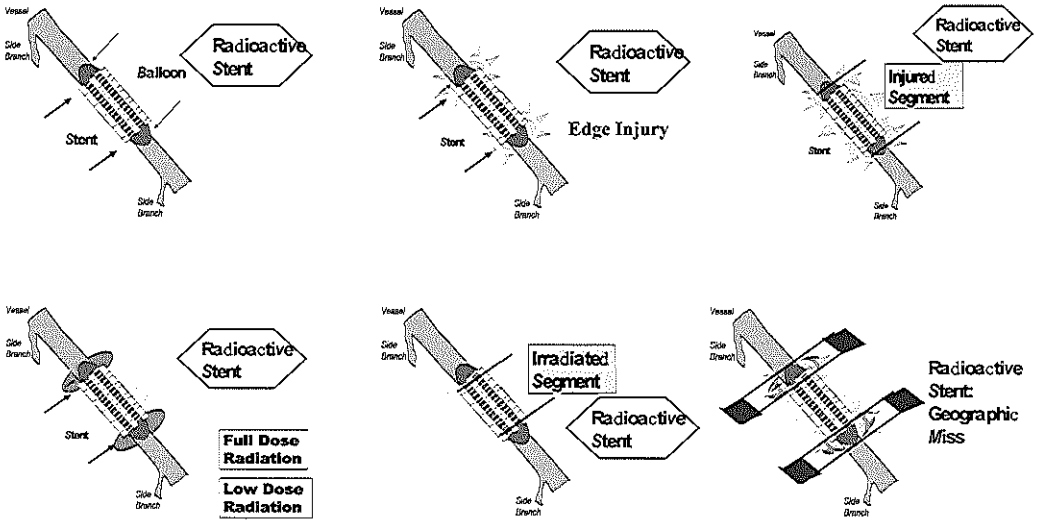
CATHETER BASED AFTERLOADING SYSTEMS

The guiding catheter should be correctly positioned at the coronary ostium: if it is to deep it will obstruct flow and may creep further into the coronary artery during the procedure, if it is to far away, it may slip during the procedure and move the source ribbon. Then the catheter accommodating the dummy source is carefully advanced into the vessel. Most radiation delivery catheter are fragile without inserted ribbon, it may easily kink during insertion. If stented lesions are treated, is has to be avoided particularly in tortuous vessels to avoid that the catheter becomes caught on the stent struts. An angiogram with the dummy source in place should be done. If angiography confirms correct positioning with complete coverage of the injured segment and safety margins, the radiation oncologist removes the dummy source, connects the afterloader device to the catheter and delivers the source. Some systems may require the withdrawal of the guide wire. The radioactive source must be filmed in place with contrast medium repeating the projections used for angioplasty. Care should be taken to not over tighten the O-ring and Y-connector while attempting to obtain good quality contrast injections, as this may crimp the delivery catheter and obstruct movement. During radiation delivery, all "unnecessary" personnel has to leave the procedure room. At the end of the dwell time, the radiation oncologists removes the source. In case of long dwell times (10-20min), the contrast medium should be withdrawn into the delivery syringe prior to injection down the coronary artery after withdrawal of the source to avoid thrombotic embolization. While removing the delivery catheter, care should be taken not to push the guide to far distally into the vessel. A final angiogram should confirm good angioplasty result and the absence of dissections and/or thrombus.

RADIOACTIVE STENT IMPLANTATION

Radioactive stents are premounted on a balloon (Figure12a). The stent (and balloon) is enclosed by a separate shield. After positioning the guiding catheter and the guide wire, the radioactive stent systems is introduced in monorail technique by means of a special shielded introducing system. It is of note, that this device design inevitably creates geographic miss, as the implantation balloon is always longer than the stent (Figure12b). Thus edge injury at the extremities of the balloon (Figure12c) is always prone to receive low-dose radiation (Figure12d-f).

Figure 12.



To minimize geographic miss, direct stenting should be performed, whenever possible. High pressure balloon inflation should be performed to assure stent expansion. Predilatation and postdilatation have to be avoided, as they carry additional risk of geographic miss at the extremities of the stent. If pre-dilatation is necessary, a balloon shorter than the stent should be used to limit the injured segment and allow for complete coverage by the stent. If postdilatation is necessary, a short (9mm) balloon should be preferred. Care has to be taken, to perform balloon inflation strictly inside the stent. Images filmed in a magnified field (5 inch) with digital zoom enhancement might be used to visualize the stent edges. Lesions with marked vessel tapering requiring proximal postdilatation should be avoided. Lesions within tortuous vessels or substantially calcified lesions should also be avoided. In these lesions, it might be impossible to advance the stent, resulting finally in "uneccessary" and "unsuccessfully" radiation exposure of patient and staff.

How to avoid geographic miss

- Source length > lesions length!
- Select a projection without foreshortening and side branch overlap
- Film any instrumentation with contrast medium to allow for anatomical orientation
- Film any instrumentation in the same projection and respiratory position
- Film the dummy and active wire in the same projection and respiratory position
- Use proximal (or distal) side branches within the vessel segment as index anatomical landmarks to assess the distances to the markers of the angioplasty balloon and the inner part of the radiopaque source markers
- Consider proximal and distal safety margins, calculated from the inner part of the radiopaque source markers
- Do not perform brachytherapy before a satisfactory angioplasty result
- Avoid instrumentation (e.g. additional stents) after brachytherapy
- Listen to your radiation oncologist!

Complications

Procedural complications

Procedural complications include all complications typically linked to the angioplasty/debulking procedure. When using radioactive stents, all complications typical for conventional stenting have to be taken into account. Most complications related to brachytherapy by removable sources are caused by the relatively high profile and stiffness of the delivery catheter:

- myocardial ischemia with angina and/or ECG changes, which, might necessitate fractionation of the dose (approx. 4% of the patients) and

T dissection after manipulation of the delivery catheter (approx. 10% of lesions)

Furthermore, radiation increases local thrombogenicity36, which promotes intracoronary thrombus formation during active treatment (approx. 4% of lesions). In these cases, GP IIb/IIIa inhibitors should be given deliberately.

Procedural Emergencies

Catheter based line sources:

Prolonged retrieval represents one of the most serious technical events which can produce unwanted dose to the patient and staff. In that first case, the entire treatment catheter should be withdrawn and placed into the bail-out box. If that is not successful, an attempt should be made to move the source into a larger diameter artery whilst calling for emergency surgery.

Balloon based fluid or gaseous sources:

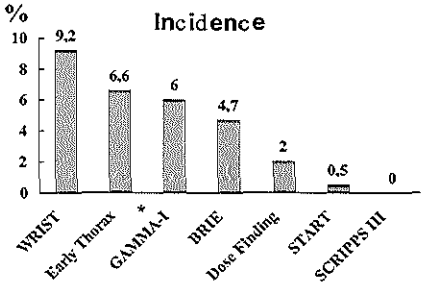
Radioactive fluid filled balloons might leak or burst and spill their contentis into the patientis blood stream. The radioactive material need to be physiologically cleared from the patient before an unacceptable dose is delivered to any tissue. Gaseous 133Xe is rapidly exhaled and presents minimum radiation hazard to the patient.

In all cases of emergency, the physicistis responsibility is to remain focused on safely retrieving the sources and minimizing unnecessary exposure of patients and staff. To allow for rapid and well directed action, contingency plans must be made in advance, discussed and rehearsed for a variety of likely and unlikely occurrences.

Postprocedural care

The arterial sheath is withdrawn immediately after the procedure and the access site sealed with a closure device (Perclose or Angioseal). In case of a difficult arterial puncture with substantial fibrosis, the sheath is removed 6 hours after the procedure and the artery manually compressed. All patients must receive effective antiplatelet therapy for at least 6 months. In our institution, we prescribe aspirin indefinitely in combination with ticlopidine (250mg twice a day) or clopidogrel (75mg daily) for 12 months. This is essential to avoid late thrombotic occlusion, which has been observed with an incidence of 0-9.2% in the early phase of catheter-based brachytherapy (Figure13)37,38 most probably due to delay in endothelialization which might increase the chance of subacute thrombosis.

Figure 13.



Incidence of late thrombotic occlusion in brachytherapy trials

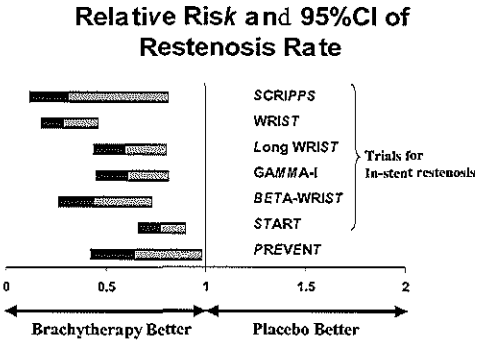
Summary of clinical trials

Catheter-based line-sources

Gamma radiation therapy is the only treatment so far showing to reduce restenosis in randomized, double blind, placebo-controlled trials (Figure14, Table1)7,26,38-40.

Figure 14. Reduction of restenosis and target vessel

revascularization rate by brachytherapy



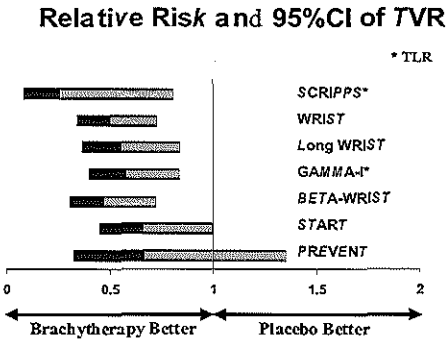


Table 1. Results of placebo-controlled gamma radiation trials at 6-month follow-up.

Study	No pts	Gy	Lesion length mm	Source	Restenosis Rate	MACE
SCRIPPS	53	8-30††	<30	Ir-192	17	15
				Placebo	54	48
WRIST	130	15*	<47	Ir-192	22	35
				Placebo	60	68
Long WRIST	120	15*	36-80	Ir-192	46	N/A
				Placebo	78	N/A
GAMMA-1	252	8-30††	<45	Ir-192	33	28
				Placebo	55	44
GAMMA-2	125	14*	< 45	Ir-192	34	30

MACE = major cardiac events, N/A = not available, No pts = number of patients.
* Dose at 2 mm from the source, †† to E.E.M.

Most of the ongoing trials use catheter-based β-radiation sources29,41,42 (Table2 and Table3). Overall, the initial target has been the treatment of de novo coronary stenosis. However, recent design trials have included patients with restenotic lesions.

Table 2. Intracoronary brachytherapy trials

Study	No pts	Dose Gy	Lesion criteria	Lesion length mm	Source	Sponsor
ARREST	50	<8, <35**	De novo	<=25	Ir-192	Vascular Therapies
ARTISTIC	50	12, 15, 18†	Instent restenosis	<=25	Ir-192	Vascular Therapies
BERT	20	12, 14, 16*	De novo	<=15	Sr/Y-90	Novoste
BERT 1.5	31	12, 14, 16†	De novo	<20	Sr/Y-90	Novoste
Betacath	1456	0, 14,18†	De novo, Restenotic	<20	Sr/Y-90	Novoste
BetaWRIST	50	20.6‡	Instent restenosis	<=47	Y-90	Boston Scientific
BETTER	150	20‡	De novo, restenotic	<=25	P-32	Radiance
BRIDGE	100	0, 20*	De novo	<=15	P-32	Guidant
BRIE	13	14, 18†	De novo, Restenotic	<20	Sr/Y-90	Novoste
Compassionate Use Rotterdam	22	16, 20†	Instent restenosis	<30	Sr/Y-90	Novoste
CURE	30	20‡‡	De novo	<22	Re-188	Columbia University
Dose Finding	181	9, 12, 15, 18‡	De novo	<15	Y-90	Schneider
GAMMA-1	252	0, 8-30††	Instent restenosis	<=45	Ir-192	Cordis
GAMMA-2	125	14†	Instent restenosis	<=45	Ir-192	Cordis
GAMMA-3	280	14†	Instent restenosis	<=45	Ir-192	Cordis
Geneva	15	18‡	De novo	<29	Y-90	Schneider
GRANITE	100	14†	Instent restenosis	<=45	Ir-192	Cordis
INDIRA	800	0, 11**	De novo, Instent restenosis	<=30	Ir-192	Cordis
INHIBIT	360	0, 20*	Instent restenosis	<44	P-32	Guidant
IRIS	37	5-12*	De novo, Restenotic	<28	P-32	Isostent

LongWRIST	120	0, 15†	Instent restenosis	>80	Ir-192	Cordis
MARS	35	20 Gy*	De novo	<20	Re-188	Mallinckrodt
PERTH	100	18‡	Instent restenosis	20-80	Re-188	Royal Perth Hospital
PREVENT	37	0, 28, 35, 42*	De novo, Restenotic, Instent restenosis	<22	P-32	Guidant
P32 Dose Response	162	45-92•	De novo, Restenotic, Instent restenosis	<28	P-32	Isostent
P32 Dose Response Cold Ends	50	22-92•	De novo, Restenotic	<15	P-32	Isostent
P32 Dose Response Hot Ends	50	71-126•	De novo, Restenotic	<15	P-32	Isostent
Radiation Stent Safety Trial	30	52-106•	De novo, Restenotic	<13	P-32	ACS
RENO	1000	14-20† 16-22†	De novo, Restenotic, Instent restenosis	Not limited	Sr/Y-90	Novoste
SCRIPPS-1	55	0, 8-30††	Restenotic	<30	Ir-192	Cordis
SCRIPPS-2	100	0, 8-30††	Instent restenosis	<65	Ir-192	Cordis
SCRIPPS-3	500	0, 14†	Instent restenosis	<81	Ir-192	Cordis
SMARTS	180	12†	De novo	<=25	Ir-192	Vascular Therapies
START	476	0, 16, 20†	Instent restenosis	<20	Sr/Y-90	Novoste
START 40/20	206	16, 20†	Instent restenosis	<20	Sr/Y-90	Novoste
SVG WRIST	120	0, 15†	SVG	<=45	Ir-192	Cordis
Venezuela	21	19-55***	De novo, Restenotic	<30	Ir-192	Non commercial
WRIST	130	0, 15†	Instent restenosis	<=47	Ir-192	Cordis

No pts = number of patients, * at 0.5 mm into the vessel wall, ** with IVUS guidance, *** at 1.5 mm from the source, † at 2 mm from the source, †† to E.E.M., • Cumulative dose over 100 days delivered to 1 mm depth outside the stent surface, •• at 3 mm from the source, ‡ at 1 mm from balloon surface, ‡‡ at media.

Table 3. Results of beta radiation trials at 6-month follow-up.

Study	No pts	Gy	Lesion length mm	Source length mm	Source	Restenosis Rate	MACE
Geneva	15	18†	<20	29	Y-90	40	33
BERT	20	12, 14, 16*	<=15	30	Sr/Y-90	15	15
BERT 1.5	35	12, 14, 16*	<20	30	Sr/Y-90	11	9
BetaWRIST	50	20.6**	<= 47	29	Y-90	34	34
					Placebo+	71	76
BRIE	149	14, 18*	<20	30	Sr/Y-90	34	34
Dose Finding Study	181	9,12,15,18**	<15	29	Y-90 9Gy	9	16
					Y-90 18Gy	26	13
PREVENT	96	16, 20, 24++	<22	27	P-32	22	26
					Placebo	50	32
START	396	18, 20*	<20	30	Sr/Y-90	29	18
					Placebo	45	25.9
Compassionate use Rotterdam	18	16, 20*	<30	30	Sr/Y-90	53	47

MACE = major cardiac events, No pts = number of patients. * Dose at 2 mm from the source, † Dose at the inner arterial surface, ** Dose at 1mm from balloon, ++ dose at 1mm into vessel wall. + 50 placebo pts from WRIST.

Radioactive stents

The clinical trials utilizing radioactive stents have been disappointing despite effective prevention of neointimal growth with the stent. Clinical and angiographic outcome has been hampered by restenosis at the edges of the radioactive stent; coined the "candy wrapper" effect25. This unfavorable phenomenon occurred irrespective of the stent design (cold end, hot end) or the dose rate (high activity vs. low activity) (Table4).

Table 4. Results of 32P radioactive stents at 6-month follow-up.

Study	No pts	Stent activity μCi	Lesion length mm	Restenosis Rate	TLR
IRIS 1A	32	0.5-1.0	<15	31	21
IRIS 1B	25	0.75-1.5	<15	50	32
IRIS Heidelberg	11	1.5-3.0	<15	54	N/A
IRIS Rotterdam	26	0.75-1.5	<28	17	12
P32 Dose Response Rotterdam	40	6.0-12	<28	44	25
P32 Dose Response Milan	23	0.75-3.0	<28	52	52
	29	3.0-6.0		41	41
	30	6.0-12		50	50
	40	12-21		30	30

N/A = not available, No pts = number of patients, TLR = target lesion revascularization.

Limitations

Low radiation doses (4-8 Gy) may stimulate neointimal proliferation. This could be due to the fact that growth factors are synthesized de novo and secreted by surviving cells. These growth factors might promote the proliferation of smooth muscle cells.

Delayed depletion of some cells (adventitial cells, fibroblast) could lead to subsequent re-population, whereby smooth muscle cells from the media could be progressively replaced by fibroblasts and extracellular matrix, leading to fibrosis, as has been previously described in animal experiments. Persistent dissections after beta-radiation have been observed at 6-month angiographical follow-up. Geographical miss, where the injured area is not completely covered by the irradiated area, is a major cause for edge restenosis. The incidence of geographical miss ranges from 18 till 34%. In case of geographical miss a restenosis rate of 39% was seen, versus 9% when there was no geographical miss. Geographical miss increases the chance of restenosis rate up to 4 times. Edge restenosis has been observed at the edges of the treated area. It appears to occur when the area injured by the balloon is larger than the irradiated area. Delayed restenosis was seen in the Condado, SCRIPPS and WRIST trial.

Future directions

Endovascular radiotherapy demonstrated to be safe and feasible over an short and mid-term perspective. There are still several unanswered questions which should be defined before determining the potential of this new technique. First, the use of β- or γ- sources or a combination of both. Secondly, the use of centering or non-centering devices. Further, to determine the best vehicle for radiation: solid (wire or train of seeds), liquid (filled-balloon) or gaseous. Finally, the target tissue must be defined as well as the minimal effective dose to be delivered. Hopefully, after the completeness of the ongoing trials in Europe as well as in the USA, many of these issues will be answered.

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Chapter 2

Routine Intracoronary Beta-Irradiation: Acute and Mid-Term (6 Months) Outcome in 100 Unselected Patients

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Routine Intracoronary Beta-Irradiation: Acute and Mid-Term (6 Months) Outcome in 100 Unselected Patients

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ABSTRACT

Aims: Intracoronary radiation is a promising therapy potentially reducing restenosis following catheter-based interventions. Currently, limited data on this treatment are available in selected patient populations. The feasibility and outcome in daily routine practice however is unknown.

Methods and results: The population consists of 100 consecutive patients (pts) with significant stenoses in 108 major epicardial arteries or bypass grafts. Intracoronary β-radiation was performed using a 90Strontium (Novoste Beta-Cath™) System. Mean age was 59±10years, 72 were males,14 diabetics, 29 had prior myocardial infarction, 45 multivessel disease, 27 unstable angina. Lesions were located in native arteries in 94%. The lesion type was B2 and C in 73%, RD 3.02±0.58mm and lesion length 24.3±15.3 mm. 37% were de novo, 44% in-stent restenotic lesions, 10% showed total occlusion. β-radiation was performed successfully in all lesions following successful angioplasty (75% stent , 21% balloon, 3% laser, 1% atherectomy) using a source length of 30mm in 36%, 40mm in 61% and 60mm in 3% of lesions. In 21 lesions a pullback procedure was done. Mean prescribed dose was 19.8±2.5Gy at 2mm from the center of the source axis. Complete coverage of the treated segment was possible in all but 9 lesions. Procedural complications were as follows: Fractionation of irradiation due to servere angina in 4 patients. Non flow-limiting thrombus formation occurred in 4 lesions, dissections in 9 lesions. During hospital stay, no death, acute myocardial infarction, or repeat revascularization was observed. At 6 months clinical follow-up, 17 patients experienced major adverse cardiac events (3 q-wave myocardial infraction, 14 target vessel revascularization).

Conclusion: In unselected clinical routine patients intracoronary catheter-based β-radiation therapy after angioplasty is safe and feasible with a high acute procedural

success. No major radiation-induced complications were observed. The clincal follow-up showed a low event rate for a patient population with complex lesions.
Key words: Brachytherapy, angioplasty, safety, radioisotopes

INTRODUCTION

Although balloon angioplasty and stent placement have become the predominant modes of coronary revascularization, restenosis remains the major limitation for catheter-based therapies. Restenosis rates in short type A and B lesions are reported to be 30%-40% for conventional balloon angioplasty and 15-30% for stents [1,2]. Coronary radiation is a promising therapy potentially reducing restenosis. Current concepts for coronary irradiation include external radiation [3], radioactive balloons [4], radioactive stents [5-7] and afterloading. Currently, limited data on this treatment are available in selected patient populations [8-10]. The safety and feasibility in daily routine application however are unknown. We report on the acute procedural and clinical success in an unselected patient population using a ^{90}Strontium/Yttrium source in patients undergoing routine angioplasty.

METHODS

Patients:

The patient population consisted of consecutive patients with angina and/or objective evidence of ischemia, who had angiographic documented coronary artery disease. Patients were included after successful treatment with conventional angioplasty and/or debulking procedures. Patients with impaired left ventricular function (LVEF <30%), undergoing or having prior chest radiotherapy, acute myocardial infarction or angiographic evidence of fresh thrombus (filling defect proximal to or involving the stenosis) prior to radiation therapy were excluded. All included patients had given written informed consent.

Angioplasty and radiation procedure:

Angioplasty was performed using routine procedures with commercially available systems and 8F guiding catheters by femoral approach. The position of all balloons, stents or debulking devices was documented angiographically. After the initial catheter-based procedure, the absence of dissection, thrombus or spasm prior to placement of the Beta-Rail delivery catheter™ was assured by contrast injection after a waiting period of 5-10 minutes.
Pre-interventional medication included non-enteric aspirin (325mg) and intravenous heparin (10 000 to 15 000 IU), in order to keep the activated clotting time >300sec during procedure. Post-interventional medication consisted of chronic aspirin and antiplatelet therapy (clopidogrel 75mg daily after a loading dose of 300mg at the day of procedure) for 3-7 months.

Intracoronary beta-irradiation was performed using a ^{90}Strontium/Yttrium source with a non-centering catheter (Novoste Beta-Cath™). Following successful angioplasty, the Beta-Rail delivery catheter was advanced over the guide wire into the vessel so that the radiopaque markers on the delivery catheter were equidistant from the center of the injured segment, with a margin of at least 7mm proximally and distally. After withdrawal of the guide wire, the source train was transported hydraulically to the distal end of the delivery catheter. The position of the source was documented angiographically. At the end of the calculated radiation time, the source was withdrawn and the Beta-Rail™ delivery catheter was removed over the guide wire. The dose was prescribed at 2mm from the source axis and adapted to the vessel diameter. Dosage calculation and the delivery of the radioactive seeds was carried out by a radiation oncologist. The length of the source train was 30mm, 40mm or 60mm. If the injured segment could not be covered completely with one source, a pullback procedure was performed. The source train was first positioned to cover the distal portion of the injured segment, then withdrawn to cover the proximal portion of the injured segment. Proximal positioning of the delivery catheter was performed using a dummy source train and overlay imaging technique. An ECG-gated video-loop, showing the distal source position was projected on the actual fluoroscopic image, done in the same projection, table position and expiration position of the patient. The delivery catheter was placed in such a way, that the radiopaque marker indicating the proximal end of the distal source overlapped with the distal marker of the proximal dummy source. After exact positioning, the dummy source was removed hydraulically and the active source train inserted.

Success:

Procedural success was defined ≤ 30% residual stenosis post procedure before removal of the guiding catheter and a successful radiation therapy procedure. *Brachytherapy success* was defined as complete (>90%) delivery of prescribed radiation dose, including dose interruption and resumption. *Clinical success* was defined as procedural success without the occurrence of major adverse cardiac events (MACE: Death, myocardial infarction, target vessel Re-PTCA or coronary artery bypass grafting (CABG)) during hospital stay.

Angiography:

On line quantitative coronary analysis was performed using the CAAS II system (Pie Medical, Maastricht, NL)[11]. All angiograms were evaluated after intracoronary administration of nitrates. The minimal lumen diameter (MLD) was determined by edge detection, reference diameter (RD) was automatically calculated by the interpolated method. The percent diameter stenosis (DS) was calculated from the minimal lumen diameter and the reference diameter.

Follow-up

Clinical follow-up has been performed within 210 days after the radiation procedure for the occurrence of MACE.

Statistical analysis

All statistical analysis was performed with commercially available software (SPSS 9.0, SPSS Inc. Chicago, Illinois). Data are presented as mean ± standard deviation, median and interquartile range or proportions. Survival analysis was done using the Kaplan-Meier method.

RESULTS

In 100 prospectively included patients 108 arteries were treated.

Patient characteristics

Patient baseline characteristics are given in TABLE 1. The population showed typical age, gender and coronary risk factor distribution. Twenty-seven patients presented with unstable angina (of whom one had acute myocardial infarction), 29 had prior myocardial infarction and 45 showed severe coronary artery disease with significant lesions in several epicardial arteries.

Lesion characteristics and angiographic data

Lesions were located in 102 native arteries (36 LAD, 28 LCx, 38 RCA) and in 6 venous bypass grafts. 40 were de-novo lesions whereas 68 lesions were restenoses, of which 47 were in-stent restenotic lesions. Lesion type was A in 4 lesions, B1 in 17, B2 in 46 and C in 33 lesions, of which 12 showed total occlusion. Lesion length was 24.3±15.3mm, with 90% lesions longer than 10mm. RD was 3.02±0.58mm and MLD 1.09±0.18mm resulting in a mean DS of 77.2±13.4%. Final RD was 3.13±0.56mm, the final MLD 2.47±0.21mm and final DS 21.2± 7.8%.

Angioplasty procedure

Angioplasty was performed in all lesions (n=108) . In 4 lesions debulking was used prior to balloon angioplasty and irradiation (3 laser, 1 directional atherectomy). Angioplasty consisted of balloon inflation in 25 lesions and stent implantation in 79 lesions. Stenting was performed electively in 80%, due to insufficient angioplasty result in 9% and due to dissection after balloon dilatation in 11%. In 39 lesions direct stenting was performed. The procedural success rate was 92%.

Brachytherapy success

Intracoronary beta-irradiation was possible in all lesions, resulting in a brachytherapy success rate of 100%. Mean prescribed dose was 19.8±2.5Gy. To cover the injured

vessel segment, a long source of 60mm was used in 3 lesions and in 21 lesions a pullback procedure was done (TABLE 2). Complete coverage with a safety margin of at least 7mm proximal and distal to the injured segment could be achieved in 99/108 lesions, thus causing geographic miss in 8.3% of the lesions.
Irradiation had to be fractionated in 4 patients due to severe angina and ECG changes indicative of myocardial ischemia. Non flow-limiting thrombus formation, successfully treated with GPIIb/IIIa inhibitors occurred in 4 lesions. Dissections were observed after manipulation of the delivery catheter in 9 lesions. Of these, 3 were Type B and C dissections, necessitating stent implantation, 6 were non flow-limiting Type A dissections not requiring further treatment.

Clinical success :

After the procedure and during hospital stay, no death, acute myocardial infarction, or repeat revascularization was observed. One patient, which underwent the procedure for acute myocardial infarction showed a raise in creatinine kinase up to 723 IU/l. Thus, clinical success rate was 91%. Median time to hospital discharge after the procedure was

Table 1:

Patient baseline characteristics

Data are presented as mean ± standard deviation or proportions of patients (n=100)

Mean age (years)	59±10
Gender (male)	72
Angina status	
Stable angina (CCS 1-4)	73
Unstable angina	27
Cardiovascular risk factors	
History of smoking	46
Diabetes mellitus	14
History of hypertension	39
History of hypercholesterolemia	58
Prior myocardial infarction, related to target vessel	29
Extent of vessel disease	
One vessel disease	55
Two vessel disease	32
Three vessel disease	13

CCS Canadian Cardiovascular Society

Table 2:

Radiation procedure

Data are presented as mean ± standard deviation or proportions of lesions (n=108)

Source length (mm)	
30	36.1
40	61.1
60	2.8
Pullback procedure (%)	19.0
Radiation dose (Gy)	
16.1	6.7
18.4	61.0
20.7	2.9
23.0	24.8
25.3	4.8
Dwell time (min)	3.34±0.44

Table 3:

In hospital major adverse cardiac and clinical events

Data are given as numbers (no) of events, no patient experienced multiple events

Event	No of events
Major adverse cardiac event (MACE)	
Death	0
Q-wave myocardial infarction	1*
CABG	0
Repeat PTCA	0
Clinical event	
Pericardial tamponade	1
Renal insufficiency	2
Isolated CK elevation	4

CABG coronary artery bypass graft
PTCA percutaneous transluminal coronary angioplasty
CK creatinine kinase

* One patient underwent the angioplasty procedure for acute myocardial infarction

2 (1;2) days. One patient, treated for a type C lesion in the medial RCA with direct stent implantation (slotted tube stent 3.0/20mm) followed by irradiation with a 30mm source developed pericardial tamponade after the procedure which was caused by an exit of the PTCA guide wire prior to irradiation. It could be successfully treated with pericardial drainage. The patient was discharged 4 days after the procedure. Two patients developed acute transient renal insufficiency after the procedure resolving after forced hydration in combination with furosemide. The further hospital stay of these patients was uneventful,

Table 4:

Major adverse cardiac events at 6 months follow-up

Data are given as numbers (no) of events and ranked (ranking) as follows: death, q-wave myocardial infarction, CABG, repeat PTCA.

Event	No of events	Ranking
Death	0	0
Q-wave myocardial infarction	3*	3*
CABG	2	2
Repeat PTCA	13	12

CABG coronary artery bypass graft
PTCA percutaneous transluminal coronary angioplasty

* One patient underwent the angioplasty procedure for acute myocardial infarction

one left the hospital 4 days, the other 10 days after the procedure. Four patients developed isolated mild creatinine kinase elevation (mean 374±123 IU/l) within 24h after the procedure without chest pain or ECG changes (TABLE 3).

Follow-up

During 6 months clinical follow-up, 17 patients experienced major adverse cardiac events, which are given in TABLE 4. Event-free survival is given in FIGURE 1. In the patient population which developed restenosis more females (40%) and diabetics (30%) were found than the total group. 14/17 patients underwent stenting at the index procedure (11 elective, 2 dissection, 1 insufficient angioplasty result) with 6 patients receiving stent-in-stent implantation. Two patients received a radiation pullback procedure. Restenosis was focal in 9 patients and located at the proximal (n=1) , the distal (n=3) or both extremities (n=5) of the index lesion.

DISCUSSION

Study population

This study describes the clinical outcome of intracoronary beta-irradiation in a large number of unselected patients. This is indicated by the relatively high proportions of patients with multivessel disease, restenosis, Type B2 and C lesions and the lesion length. Thus, our series is more likely to reflect "real world" lesions in a tertiary care center than the highly selected patient populations in previously reported trials. The generalizability of study results plays an important role on the background that the number of centers licensed for intracoronary radiation therapy is growing rapidly since the first patient in Europe has been randomized in 1997 at our centre.

Feasibility in the "real world"

Brachytherapy was applied routinely with excellent success rate. The prescribed radiation dose could be delivered to all lesions. Special care was taken to cover the complete injured vessel segment in order to avoid "geographic miss", the deleterious effect of balloon induced injury and low dose radiation at the extremities of the source train [12]. To overcome this potential limitation of intracoronary irradiation, sequential pullback or combination of source trains with different length was performed in a relatively high proportion of patients.

Procedural complications

No acute or subacute major adverse cardiac events or irradiation induced major complications were seen. The procedural costs, however, raised substantially from a mean of 3200.- Euro for conventional coronary angioplasty procedures (1/2000 - 5/2000) to 4100.- Euro. Thus, the cost-effectiveness of intracoronary brachytherapy still needs to be proven.

Our findings are in accordance with previous published data [9] on various afterloading techniques. In some of these series, however, irradiation induced adverse events were reported. Using a 192 Iridium source, Condado describes successful gamma-radiation delivery in all 21 patients following balloon angioplasty, however, one patient developed prolonged coronary spasm, an other patient suffered subacute thrombosis [13], whereas in another series of 26 patients with restenotic or in-stent restenotic lesions no in hospital adverse events were seen [8] . In a larger patient cohort (n=130) undergoing randomized gamma irradiation for in-stent restenosis, 2 patients in the placebo and 2 patients in the radiation group required fractionation of radiation due to angina and ischemia, 2 patients required vascular access site repair and 8% of patients had CKMB elevation [14]. Similarily, dose fractionation due to ischemia was required in 11/50 patients receiving

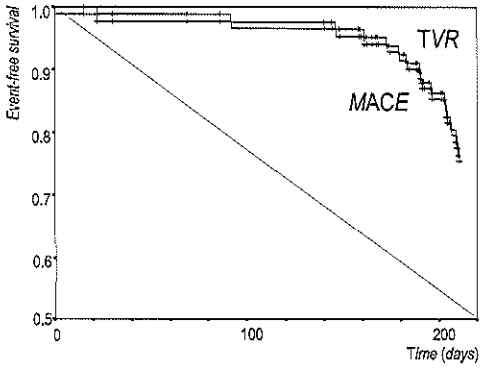

Figure 1

Event free survival at 6 months follow-up (Kaplan -Meier). TLR indicates target lesion revascularization and includes repeat PTCA and CABG. MACE indicates major adverse cardiac events. Events are given ranked as follows: death, q-wave myocardial infarction, CABG, repeat PTCA.

beta-afterloading with a centered device for in-stent restenosis [15], indicating insufficient distal perfusion with the centering balloon during irradiation as it was also seen in 4/15 patients in the Geneva series [16]. In our study with a non-centered device, dose fractionation was necessary in 4/108 lesions only.

Thrombus:

The most frequently seen possible irradiation associated events were thrombus formation and dissections. In our series, in 4 lesions intracoronary thrombus formation during the procedure could be visualized as a contrast filling defect by angiography. In all 4 lesions, thrombus formation was not flow-limiting. All patients received intravenously GP IIbIIIa inhibitors for 12h, their in-hospital course was uneventful, without evidence for (sub-)acute thrombosis.

Dissection:

In 9/108 lesions dissections were documented angiographically at the end of the irradiation procedure. In 3/9 lesions, further preventive stent implantation was performed [17]. However, the prognostic impact of non flow-limiting dissections in patients undergoing brachytherapy in poorly understood. Previous case series (16 patients each) with acute dissection following balloon angioplasty and intracoronary beta-irradiation have shown that these dissections persist in approximately 50% of the patients [18,19] at six months follow-up. Persisting dissections were not associated with a change in angina status or any acute or subacute clinical sequelae [19]. In contrast 2/6 patients presenting sudden thrombotic events after balloon angioplasty and beta irradiation showed a Type B dissection after the procedure [20]. No correlation between persistence of dissection and the prescribed dose was seen [18].

Mid-term outcome

In our series, the mid-term outcome seems comparable to randomized studies despite a higher a priori restenosis risk of our study population. Two patients experienced myocardial infarction, possibly caused by increased thrombogenicity and prolonged wound healing reported in experimental [21-23] and clinical series [20]. Clinically driven target vessel revascularization has been performed in 15% of the patients. This is as expected somewhat higher than recently reported 11% for *short, de-novo* lesions treated with beta-irradiation [24].

In unselected patients intracoronary catheter-based β-radiation therapy after angioplasty is safe and feasible with a high acute procedural success. No major radiation-induced complications were observed. The clinical follow-up showed a relatively low event rate for a patient population with complex lesions.

Limitations

This is a non-randomized, non placebo controlled mono-centre experience. We evaluated only one type of beta radiation delivery catheter, thus these results can not be

extrapolated to other radiation (e.g. centering) delivery systems or other (e.g. gamma) sources. These data are restricted to the in mid-term outcome (6 months). Possibly radiation induced delayed restenosis needs to be further investigated. The small number of events in this study does not allow to identify patient or lesion related factors predicting adverse procedural outcome.

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Part I-B

The Rise of Brachytherapy

Mechanistic Interpretation of Brachytherapy

Chapter 3

Initial Observation Regarding Changes in Vessel Dimensions after Balloon Angioplasty and Stenting Followed by Catheter-Based β- Radiation Is stenting necessary in the setting of catheter-based radiotherapy?

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Initial Observation Regarding Changes in Vessel Dimensions after Balloon Angioplasty and Stenting Followed by Catheter-Based β- Radiation Is stenting necessary in the setting of catheter-based radiotherapy?

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ABSTRACT

Aims

We sought to compare the effect of intracoronary β-radiation on the vessel dimensions in *de novo* lesions using three-dimensional IVUS quantification after balloon angioplasty and stenting.

Methods and Results

Forty patients (44 vessels; 28 balloon angioplasty and 16 stenting) treated with catheter-based β-radiation and 18 non-irradiated control patients (18 vessels; 10 balloon angioplasty and 8 stenting) were investigated by means of three-dimensional volumetric IVUS analysis post-procedure and at 6-8 months follow-up.

Total vessel (EEM) volume enlarged after both balloon angioplasty and stenting (+37 mm^3 versus +42 mm^3, p=NS), but vessel wall volume (plaque plus media) also increased similarly (+33 mm^3 versus +49 mm^3, p=NS) in the irradiated patients. Lumen volume remained unchanged in both groups (+3 mm^3 versus -7 mm^3, p=NS). In the stent-covered segments, neointima at follow-up was significantly smaller in the irradiated group than the control group (8 mm^3 versus 27 mm^3, p=0.001, respectively), but the total amount of tissue growth was similar in both groups (33 mm^3 versus 29 mm^3, p=NS).

Conclusions

Intracoronary β-radiation induces vessel enlargement after balloon angioplasty and/or stenting, accommodating tissue growth. Additional stenting may not play an important role to prevent constrictive remodeling in the setting of catheter-based intracoronary β-radiotherapy..

We investigated the effect of intracoronary β-radiation in *de novo* lesions using 3D-IVUS after balloon angioplasty (BA) and stenting. Consecutive patients (28 BA and 16 stenting) treated with β-radiation and 18 non-irradiated patients (10 BA and 8 stenting) were investigated. Total vessel (EEM) and vessel wall (plaque+media) volume increases were similar after both BA and stenting leaving the lumen volume unchanged. In the stent-covered segments, neointimal hyperplasia was smaller in the irradiated group than control, although the total tissue growth was similar. BA and/or stenting followed by intracoronary β-radiation induces vessel enlargement accommodating tissue growth.

Key Words
Coronary angioplasty, stent, brachytherapy, intravascular ultrasound

INTRODUCTION

The safety and feasibility of catheter-based intracoronary γ or β-irradiation has been established in clinical trials(1-3). Randomized studies have demonstrated the reduction of restenosis in patients with restenotic lesions(4,5). Recently, β-irradiation has shown to inhibit the recurrence of restenosis(6)Popma ACCIS 2000 presentation, START trial). A non-randomized study using β-radiation to treat *de novo* coronary lesions has also shown promising results in the reduction of restenosis rate after balloon angioplasty(7). It is of note that European experiences have been more oriented to β-radiation for de novo lesions, whereas in the U.S., most efforts have been focusing on the γ-radiation for in-stent restenosis(8).

Restenosis after angioplasty is caused by two components: vessel remodeling and neointimal formation. Data from experimental models have demonstrated the inhibition of neointimal formation and of constrictive negative remodeling after intracoronary radiation(9-12). Recently, these findings were confirmed in human coronary arteries using sophisticated three-dimensional volumetric intravascular ultrasound (IVUS) (13). In this era of stent implantation, the effect of brachytherapy in stented arteries deserves careful evaluation, and one small study has suggested that an increase in plaque volume occurred after brachytherapy mainly outside the stent(14).

The aim of the present study was to investigate the effect of intracoronary β-radiation on the vessel dimensions of *de novo* lesions after balloon angioplasty and stenting using three-dimensional IVUS quantification.

METHODS

Patients

From April/97 to May/99, 64 *de novo* lesions (57 patients) were consecutively treated with catheter-based intracoronary ß-radiation using the Beta-Cath System™ (Novoste Corp., Norcross, GA). IVUS analyses of 10 vessels (7 patients) were not included in this study due to the implantation of multiple overlapping stents outside the irradiated segments because of the inability to define the region of interest. Additional 10 vessels (10 patients) were not included because 3-dimensional-IVUS analysis was not performed either post-procedure or at follow-up (3 patients had severe restenosis, 1 patients met IVUS crossing failure at baseline, 3 presented thrombotic occlusion, and 3 other patients refused follow-up angiograms). The control group consists of 18 patients successfully treated with conventional balloon angioplasty (n=10) or single stent implantation (n=8) during the same period. In these patients, the radiation delivery catheter was also introduced in the target coronary arteries, but a dummy source was used instead of radioactive source as placebo groups for brachytherapy trials.

The study population consists of 40 irradiated patients (44 vessels; 28 treated with balloon angioplasty and 16 treated with stenting) and 18 non-irradiated placebo patients

(18 vessels). Patients presented with angina pectoris or positive stress testing. Patients with myocardial infarction within 72 hours prior to treatment or left ventricular ejection fraction < 30% were not included in this study. Angiographic inclusion criteria consisted of a reference vessel diameter > 2.5 mm and < 4.0 mm and a lesion length < 20 mm. Only slotted tube stents were used for this study.

The Medical Ethics Committee of the University Hospital Rotterdam Dijkzigt approved the protocol of intracoronary radiation. All patients gave written informed consent.

Radiation System

The source train of the Beta-Cath™ System consists of a series of 12 independent cylindrical seeds, which contain pure ß-emitting $^{90}Sr/^{90}Y$, and is bordered by 2 gold markers (30mm total length of radioactive seeds). The profile of the catheter is 5 French and the source train is not centered. The radiation sources remain at the treatment site for approximately 2-4 minutes to deliver a predetermined dose at 2mm from the centerline of the axis of the source train. Prescribed radiation doses were 12Gy (8 vessels), 14Gy (12 vessels), 16 Gy (9 vessels), and 18Gy (15 vessels).

Procedure

All patients received aspirin (250 mg/day) and heparin IV (10.000 IU) during the procedure and additional heparin was given to maintain the activated clotting time >300sec. Stented patients also received ticlopidine (250mg/day) or clopidgrel (75mg/day) for at least one month. Balloon angioplasty was performed according to standard clinical practice. After successful angioplasty, intracoronary β radiation was performed as previously described, (1) and repeat angiography and IVUS pullback were carried out. If the result was suboptimal (> 30% diameter stenosis), or if the patient was assigned to provisional stenting, the stent was implanted with high-pressure post-dilatation and IVUS guidance. Finally, repeat angiography and IVUS were carried out. Intracoronary isosorbide dinitrates (200 µg) were administered immediately prior to each of the IVUS pullbacks. At follow-up (6-8 month), further IVUS analysis of the treated vessel was performed.

IVUS image acquisition and quantitative analysis

The coronary segment subject to 3-dimensional reconstruction was examined with a mechanical IVUS system (CVIS, Boston Scientific Corporation, Maple Grove, MN) with a sheath-based IVUS catheter incorporating a 30 MHz single-element transducer rotating at 1800 rpm. ECG-gated image acquisition and digitization was performed by a workstation designed for the 3-D reconstruction of echocardiographic images (EchoScan, Tomtec, Munich, Germany). Description of this system has been reported in detail elsewhere(15-17). In brief, the steering logic of the workstation considered the

heart rate variability and only acquired images from cycles meeting a predetermined range and coinciding with the peak of the R wave.

A Microsoft Windows™-based contour detection program, developed at the Thoraxcenter, was used for off-line volumetric quantification ADDIN ENRfu (18). Briefly, this program constructed longitudinal sections from the data set and identified the contours corresponding to the lumen, media and stent boundaries. Volumetric data were calculated by the formula: $V= \sum_{i=1}^{n} A_i * H$, where V = volume, A = area of EEM (external elastic membrane), lumen, stent or plaque in a given cross-sectional ultrasound image, H = thickness of the coronary artery slice, that was reported by this digitized cross-section, and n = the number of digitized cross-sectional images encompassing the volume to be measured. Checking and editing of the contours of the planar images were performed by two independent experienced analysts (KK, MC). Intra-observer variability assessed by analyzing IVUS volumetric studies at least 3 months apart has been reported:-0.4 ± 1.1% in lumen volume, -0.4 ± 0.6% in total vessel (EEM) volume and -0.3 ± 1.0% in vessel wall (plaque+media) volumes using motorized ECG-gated pullback(17). The application of this system has been reported in clinical studies(13,14,19,20).

The methodology to define the segment of interest has also been described previously(13,14,21). An angiogram with contrast injection was performed after positioning the radiation delivery catheter in the study group and a deflated balloon in the control group during the procedure. By the use of the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands), each angiographic sequence showing the radiation delivery catheter or the deflated balloon during contrast injection can be displayed on the screen with ECG tracing. By selecting those frames in the same part of the cardiac cycle, we were able to define the location of the radiation source train, balloon inflations and their relationship with anatomical landmarks. Typically, the aorto-ostial junction, stent and/or side-branches were used as landmarks. The anatomical landmark closest to either of the balloon markers was used as a reference point. During the subsequent IVUS imaging, this reference point was recognized and used for selecting the area of interest: a 30-mm long segment irradiated by the radioactive or sham source train. At follow-up, correct matching of the region of interest was assured by both the use of the same IVUS motorized pull-back system and comparison of the longitudinal view to that of post-procedure. In the radiation group, a 26-mm segment which we considered as fully irradiated was selected by excluding both 2-mm ends of the 30-mm segments between the 2 gold markers, because this radiation source has an acute dose fall-off starting at the last seeds(22). Similar analysis was performed in the control group. In stented vessels, a specific analysis only within the segment covered by the stent was also performed.

Total vessel (EEM), lumen and stent volumes were calculated from the contours of each cross-sections by the software as stated above. In-vivo measurement of neointimal

formation after stenting has been previously validated(23). The assessment of external elastic membrane in stented patients has been reported(14). When the EEM boundary was not visible in a single cross-sectional view, the computer interpolated it from the contours of the immediately previous and following cross-sections. In addition, the use of three-dimensional reconstruction with multiple longitudinal views facilitated the visualization of vessel structures outside the stent. In all cases, the stented segment was covered by the radiation or dummy source.

Since it is usually impossible to distinguish the intima and media by IVUS, vessel wall volume (plaque plus media), tissue growth inside stent and vessel wall volume outside the stent was calculated as the representatives of tissue growth.

Vessel wall volume (plaque plus media) = Total vessel (EEM) volume
– Lumen volume

Tissue Growth Inside Stent = Stent volume – Lumen volume within stent

Vessel wall volume outside the stent = Total vessel volume of stent-covered segment
– stent volume

In order to assess the volumetric changes of the vessel structures after 6-8 months, the delta value for each measurement was calculated (delta (Δ) = follow-up – post-procedure). To eliminate the influence of the vessel size and the length of the analyzed segment, percent change (delta volume / post-procedure volume) was also calculated.

Remodeling of the vessel wall was considered when total vessel (EEM) volume increased or decreased, compared to post-procedure measurements by at least two standard deviations (± 1.2%) of the intra-observer variability. By using this technique, the potential intrinsic error of the method may be avoided(24,25).

Statistical analysis

Quantitative data are presented as mean ± standard deviation. The comparisons between the volumetric data were performed using the two-tailed, paired or unpaired Student's t-test. Categorical data were compared by means of Fisher's exact test. A value of $p<0.05$ was considered statistically significant.

RESULTS

Baseline clinical characteristics were similar between irradiated and control patients (Table 1). Lesion location was also similar between the irradiated and control groups (RCA 34% vs 39%, LAD 41% vs 39%, LCX 25% vs 22%, respectively).

Clinical data

No death and myocardial infarction was observed in the study populations. Restenosis (%diameter stenosis > 50% by quantitative coronary angioplasty) was observed in 6

Table 1. Baseline Patient Characteristics

	Radiation (n=40)	Control (n=18)	p value
Age	56 ± 10	58 ± 9	NS
Sex (male, %)	32 (80%)	14 (78%)	NS
History of MI	26 (65%)	9 (50%)	NS
Diabetics	4 (10%)	2 (11%)	NS
Hypertension	14 (35%)	3 (17%)	NS
Dyslipidemia	20 (50%)	7 (39%)	NS
History of smoking	26 (65%)	11 (61%)	NS
Family history of CAD	17 (43%)	24 (44%)	NS
Angina CCS III/VI	14 (70%)	14 (78%)	NS

CAD= Coronary artery disease, CCS= Canadian Cardiovascular Society Angina Class, MI= myocardial infarction

Table 2. Volumetric IVUS data

	Radiation		Control	
	Balloon n=28	Stent n=16	Balloon n=10	Stent n=8
Analyzed length	25.8 ± 0.2	25.8 ± 0.2	24.8 ± 1.2	26.0 ± 0
Stent length		16.0 ± 3.2		15.2 ± 1.7
Lumen volume				
Post	216 ± 91	217 ± 64	228 ± 145	215 ± 87
Follow-up	219 ± 102	210 ± 73	203 ± 138	173 ± 64
p-value	0.7	0.4	0.024	0.006
Total vessel volume				
Post	390 ± 122	456 ± 131	411 ± 186	443 ± 126
Follow-up	426 ± 139	498 ± 158	408 ± 194	430 ± 123
p-value	0.002	0.003	0.8	0.3
Vessel wall volume				
Post	174 ± 48	239 ± 76	183 ± 70	228 ± 55
Follow-up	207 ± 58	288 ± 92	206 ± 93	256 ± 72
p-value	<0.001	<0.001	0.09	0.009
Stent volume		140 ± 47		126 ± 41
NIH within stent		8 ± 8		27 ± 14

NIH = neointimal hyperplasia

out of 28 lesions (21%) in the irradiated balloon group and 4 out of 16 lesions (25%) in the irradiated stent group. Target lesion revascularization rates were 14% in the balloon group and 25% in the stent group. In the control group, 2 lesions (20%) in the balloon group and 2 lesions (25%) in the stent group presented restenosis. Target lesion revascularization rates in the control groups were 10% and 12.5%, respectively.

Balloon versus Stent within the irradiated segment

There was no difference of baseline characteristics between balloon and stented patients. Volumetric data are demonstrated in Table 2. In the irradiated patients, EEM volume and vessel wall volume increased significantly by the paired t-test in both balloon and stented vessels during follow-up as shown in Figure 1. The degree of EEM volume increase was similar between the balloon group and the stent group (+36.6 mm^3 versus +42.3 mm^3, p=NS). Accordingly lumen volume remained unchanged in both groups (215.9 mm^3 to 219.4 mm^3 in the balloon group, 217.2 mm^3 to 210.1 mm^3, in the stent group, p=NS for both groups). Similar correlations of the % changes in lumen dimensions, tissue growth and vessel enlargement have been observed between balloon treated and stented vessels (Figure 2).

Irradiated versus Control

Percent changes in IVUS parameters are presented in Figure 3. In both balloon angioplasty and stenting vessels, positive remodeling (enlargement of the EEM volume)

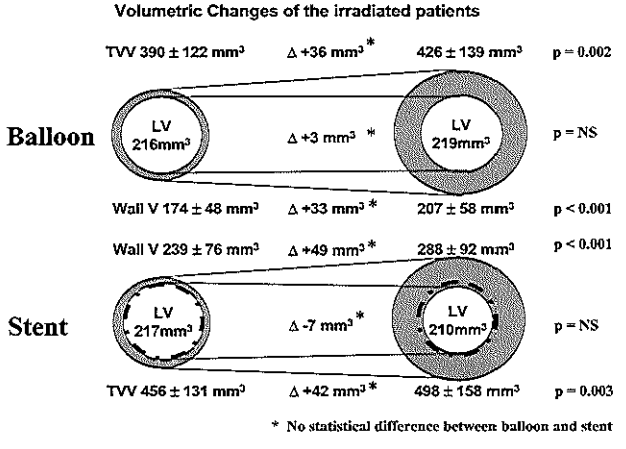

Figure 1
Volumetric changes of the irradiated patients after balloon angioplasty and stenting.
Data are compared by the paired t-test.
TVV = total vessel volume (bordered by external elastic membrane),
Wall V = vessel wall volume (intima+media)
LV = lumen volume
* = No statistical difference between balloon angioplasty and stenting

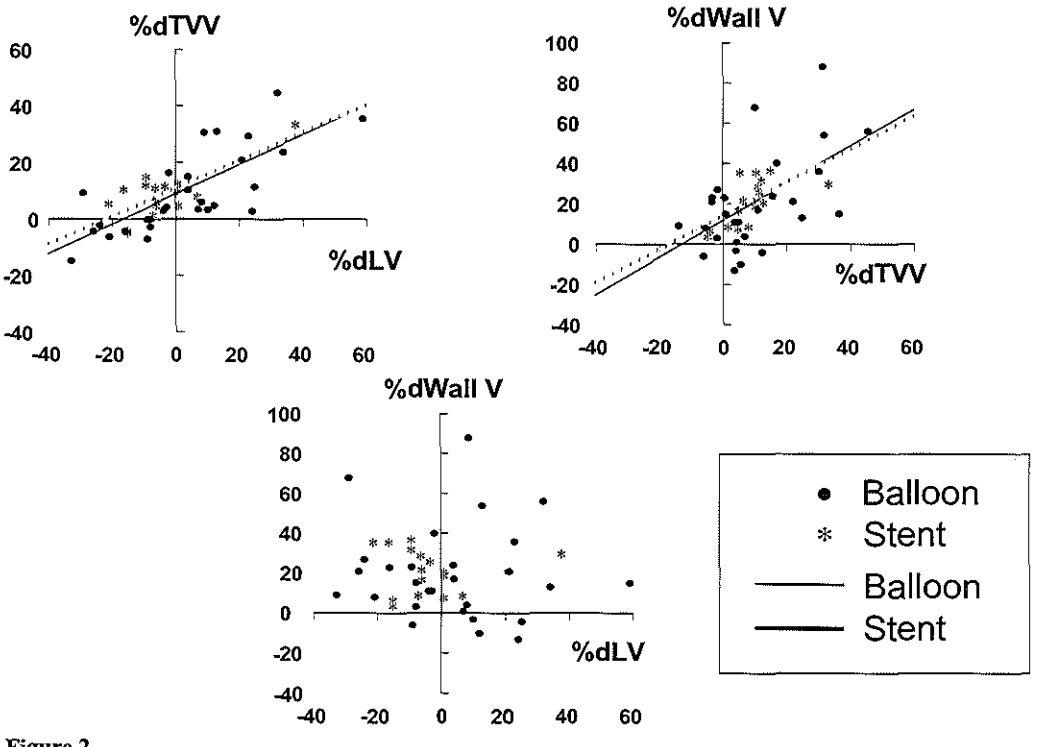

Figure 2
Correlations between the changes in lumen change, total vessel volume, and tissue growth in the irradiated vessels.
Upper left panel: Correlation between % changes in lumen volume and total vessel volume. Significant relationships have been observed both in the balloon group ($r=0.77$, $p<0.001$) and in the stent group ($r=0.76$, $p=0.001$).
Upper right panel: Correlation between % changes in total vessel volume and vessel wall volume. Significant correlations have been observed both in the balloon group ($r=0.57$, $p=0.002$) and in the stent group ($r=0.63$, $p=0.009$).
Lower panel: Correlation between % changes in lumen volume and vessel wall volume. No correlation has been observed either in balloon or stent group.
dTVV = change in total vessel volume (bordered by external elastic membrane),
dWall V = change in vessel wall volume (intima+media)
dLV = change in lumen volume

was observed more frequently in the irradiated group than in the control group (68% vs 30%; p=0.044, in balloon treated vessels, 88% vs 25%; p=0.005 in stented vessels). In the balloon treated segments, vessel enlargement fully compensated the vessel wall volume increase so that lumen even increased (+3.4%) in the irradiated vessels (Figure 3). In stented vessels of irradiated patients, vessel wall volume increased despite inhibition of tissue growth inside stent (Figure 3), owing to the total vessel volume increase. Thus lumen reductions were more pronounced in the control vessels than in the irradiated vessels after both balloon angioplasty and stenting (Figure 3).

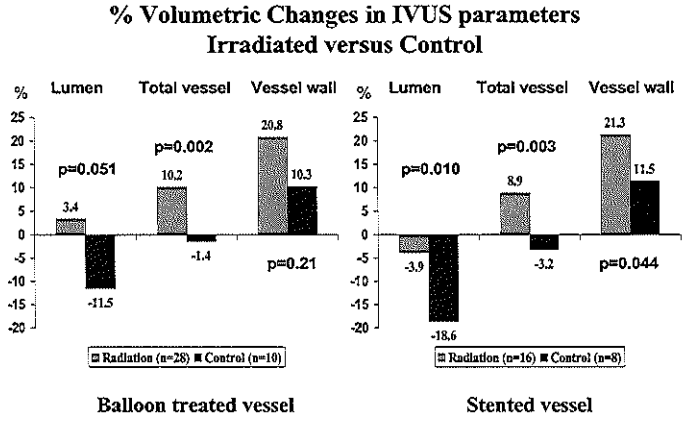

Figure 3
Percent volumetric changes in IVUS parameters within fully irradiated segments. Comparison between irradiated and control vessels.

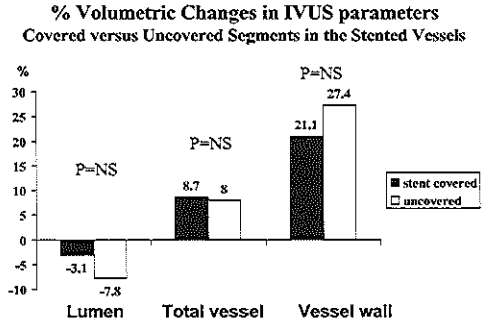

Figure 4
Percent volumetric changes in IVUS parameters in stented vessels. Comparison between stent-covered and uncovered segments within fully irradiated segments.

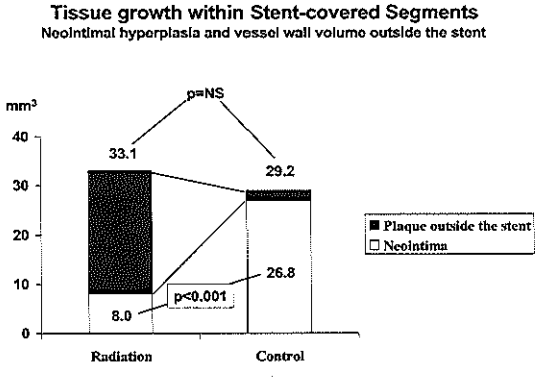

Figure 5
Tissue growth (neointimal hyperplasia and vessel wall volume increase outside the stent) within stent-covered segments. Comparison between irradiated and non-irradiated vessels.

Neointimal hyperplasia and vessel enlargement in stented vessels

Percent reduction in lumen volume in segments not covered by the stent was similar to that in the irradiated segments covered by stent (-3.1% versus –7.8%, p=NS) as shown in Figure 4. Total vessel (EEM) volume and vessel wall volume also increased similarly in both segments.

In the stent-covered segments, tissue growth inside stent at follow-up was significantly smaller in the irradiated group than in control group (8.0±7.9 mm^3 versus 26.8±13.8 mm^3, p=0.001, respectively), although total amount of tissue growth was similar in both groups (Figure 5). Different pattern of the tissue growth distribution was observed between irradiated and non-irradiated vessels. In the irradiated vessels, tissue growth mainly occurred outside of the stent (25.1 out of 33.1 mm^3), whereas most of the tissue increase in control vessels was represented by tissue growth inside stent (26.8 out of 29.2 mm^3) as demonstrated in Figure 5.

DISCUSSION

This 3-D volumetric IVUS study demonstrates that catheter-based β-radiation induces vessel enlargement after both balloon angioplasty and stenting comparing with control. Positive remodeling was the main mechanism of preserving lumen volume after balloon angioplasty in the irradiated patients. In the stented vessels, neointimal formation was inhibited and lumen preserved in the irradiated segments. However vessel wall volume significantly increased outside the stent in the irradiated vessels.

It has been reported that vessel shrinkage is mainly responsible for restenosis after conventional balloon angioplasty(26-29). It has been shown that intracoronary radiation inhibited neointimal proliferation in most of experimental models(30-33). In addition, experimental data have also suggested that radiation have an effect on vessel remodeling by modifying cell responses in the adventitia. (11,12) In the irradiated group, 35 vessels (80%) had an increase in total vessel (EEM) volume. The thinning of adventitial layer by radiation may be one of the explanations for this phenomenon, although it is still controversial(33,34).

In stented segments, the change in lumen volume was similar to that in non-stented segments in the irradiated vessels. Furthermore, lumen was preserved regardless of the stent presence. These findings suggest that coronary stent is not necessary for lumen maintenance in the setting of catheter-based radiation. Considering the fact that the combination of stent and radiation has been associated with late thrombosis(34-36) and late stent malapposition(37), the implantation of coronary stents in the setting of intracoronary radiotherapy may be discouraged, unless it is in a bail-out situation.

Judging from the results in the stented vessels, it seems that tissue grows only outwards after intracoronary irradiation and results in enlargement of the total vessel (Figure 5). It has been suggested that intravascular radiation decreases myofibroblast differentiation in the adventitia and reduces cell proliferation without affecting apoptosis(12). Fareh

has reported that β-radiation caused vascular smooth muscle cells to remain G_0/G_1 phase and the growth arrest was maintained over 5 days. It has also been reported that the migratory function may be more radiosensible than their proliferative response(38). In our previous report, the average delivered dose at the adventitia was only 5 Gy using the same system. Therefore, it may be possible that considerable segments receive lower dose than the effective dose for the inhibition of tissue growth, while those doses are sufficient for the inhibition of migration in this study. The presence of stent metal keeps stimulating the cellular response when the effect of radiation diminishes one week after the procedure(11). It has been shown that migration of smooth muscle cells into the intima did not contribute to lesion growth during the second week after injury(39). Thus, the second wave of cellular proliferation may not be inhibited by the catheter-based radiation, and tissue proliferation may be more frequent on the outer layer of the media close to the adventitia rather than intima in the irradiated vessels when migration of proliferative cells are inhibited. Further immuno-histochemical investigation is necessary to elucidate the mechanism of this finding.

Limitations

In human studies, it is almost impossible to distinguish the intima and media using IVUS. The enlargement of the echogenic marker at outer layer of media is assumed as positive remodeling.

This study is not based on the actual dose calculated by the distance from the center axis to adventitia. Heterogenic distribution of the delivered dose, which is related with a plaque growth, has been previously demonstrated in the setting of catheter-based β-radiation ADDIN ENRfu (20). Accurate dosimetry will provide important information to the mechanism of remodeling and plaque increase process.

Studies using IVUS are limited in cases where severe restenosis is present. However, only 3 patients were not included in this study because of this reason. Vessels with multiple stents (n=10) were excluded from analysis, since multiple stent deployment with overlapping or gap between stents may be a confounding factor in the mechanistic interpretation of our results.

CONCLUSIONS

Intracoronary β-radiation induces vessel enlargement after balloon angioplasty and/or stenting, accommodating tissue growth. Additional stenting may not play an important role to prevent constrictive remodeling in the setting of catheter-based intracoronary β-radiotherapy.

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Chapter 4

Three-dimensional Intravascular Ultrasound Assessment of Non-Injured Edges of ß-Irradiated Coronary Segments

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Three-Dimensional Intravascular Ultrasound Assessment of Noninjured Edges of β-Irradiated Coronary Segments

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Background—The "edge effect," late lumen loss at the margins of the treated segment, has become an important issue in the field of coronary brachytherapy. The aim of the present study was to assess the edge effect in noninjured margins adjacent to the irradiated segments after catheter-based intracoronary β-irradiation.

Methods and Results—Fifty-three vessels were assessed by means of 3-dimensional intravascular ultrasound after the procedure and at 6- to 8-month follow-up. Fourteen vessels (placebo group) did not receive radiation (sham source), whereas 39 vessels were irradiated. In the irradiated group, 48 edges (5 mm in length) were identified as noninjured, whereas 18 noninjured edges were selected in the placebo group. We compared the volumetric intravascular ultrasound measurements of the noninjured edges of the irradiated vessels with the fully irradiated nonstented segments (IRS, n=27) (26-mm segments received the prescribed 100% isodose) and the noninjured edges of the vessels of the placebo patients. The lumen decreased (6 mm^3) in the noninjured edges of the irradiated vessels at follow-up (P=0.001). We observed a similar increase in plaque volume in all segments: noninjured edges of the irradiated group (19.6%), noninjured edges of the placebo group (21.5%), and IRS (21.0%). The total vessel volume increased in the IRS in the 3 groups. No edge segment was subject to repeat revascularization.

Conclusions—The edge effect occurs in the noninjured margins of radiation source train in both irradiated and placebo patients. Thus, low-dose radiation may not play an important role in this phenomenon, whereas nonmeasurable device injury may be considered a plausible alternative explanation. **(*Circulation*. 2000;102:1484-1489.)**

Key Words: brachytherapy ■ angioplasty ■ ultrasonics

The "edge effect," a lumen loss at the segments adjacent to the treated site, is a new phenomenon in the field of interventional cardiology. Although it may also occur after conventional treatment (ie, stent implantation),[1,2] it has become an important issue after the introduction of intracoronary brachytherapy in clinical practice.

Recently, the edge effect was reported in patients who received radioactive stents with intermediate activity (3 to 12 μCi). Neointimal formation was inhibited in a dose-dependent manner within the stented area, but proliferation and unfavorable remodeling were demonstrated at the stent margins .[3] The authors dubbed this angiographic finding as the "candy-wrapper" effect. Further, the edge effect has been observed in patients treated by means of catheter-based β-radiation.[4,5] In a 3-dimensional (3-D) volumetric intravascular ultrasound (IVUS) investigation, our group observed a decrease in lumen volume at the edges of the irradiated segment due to an increase in plaque volume not accommodated by vessel enlargement.[5] In all 3 reports, the authors hypothesized that the edge effect was due to the combination of low-dose radiation and balloon-induced injury in the segments adjacent to the irradiated site. Indeed, the potential stimulatory effect of low-dose radiation after injury has been demonstrated in animal studies.[6,7]

In consideration that the coronary segments adjacent to the irradiated site will invariably receive a lower dose of radiation to some extent, an important issue remains to be clarified: Does the edge effect also occur in noninjured segments? To address this issue, we (1) assessed the midterm (6 to 8 months) geometrical change of the noninjured edge segments in the irradiated coronary vessels and (2) compared these edge segments with both irradiated segments (IRS) and nonirradiated (sham source), noninjured coronary segments by means of a volumetric 3-D IVUS assessment.

Methods

Study Population

From April 1997 to March 1999, 56 de novo lesions of 50 patients were treated with catheter-based intracoronary β-radiation with the Beta-Cath System (Novoste Corp). IVUS analyses of 10 vessels (7

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From the Thoraxcenter (K.K., M.A.C., M.S., I.K., P.S., J.M.R.L., P.W.S.), University Hospital Rotterdam Dijkzigt, the Netherlands; and Daniel den Hoed Cancer Center (J.P.A.M., V.L.M.A.C., P.C.L.), Rotterdam, the Netherlands.

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patients) were not included in this study due to the implantation of multiple stents overlapping outside the irradiated area. In addition, 3-D IVUS analysis was not carried out either after the procedure or at follow-up in 7 vessels (7 patients): 2 had severe restenosis (1 diffuse restenosis, 1 in-stent restenosis, not related to their edges), 3 presented with thrombotic occlusion, and 2 other patients without recurrent angina refused follow-up angiography. The placebo group consists of 14 patients who were successfully treated with conventional balloon angioplasty or single-stent implantation during the same period. In these patients, the radiation delivery catheter was also introduced into the target coronary arteries, but a dummy source train was used instead of radioactive source according to randomization.

Thus, the study population consists of 36 irradiated patients (39 vessels) and 14 nonirradiated placebo patients (14 vessels) who underwent successful 3-D ECG-gated IVUS analysis immediately after the procedure and at follow-up. Patients were treated due to ischemia-related symptoms or positive stress testing. Those with myocardial infarction within 72 hours before the treatment or a left ventricular ejection fraction of <0.30 were not included in the study. Angiographic inclusion criteria consist of a reference vessel diameter of >2.5 mm and <4.0 mm and a lesion length of <20 mm.

The Medical Ethics Committee of the University Hospital Dijkzigt approved the use of intracoronary radiation. All patients gave written informed consent.

Radiotherapy System

The source train of the Beta-Cath System consists of a series of 12 independent cylindrical seeds that contain pure β-emitting $^{90}Sr/^{90}Y$ and is bordered by 2 gold markers (30 mm in length). The longitudinal distance of the "full" prescribed dose (100% isodose) coverage measured with radiochromic films is ≈26 mm (Novoste Corp, data on file, personal communication). The profile of the catheter is 5F, and the source train is not centered.

Procedure

All patients received aspirin (250 mg/d) and heparin IV (10 000 IU) before the procedure, whereas stented patients also received ticlopidine (250 mg/d) for 30 days. Heparin was administered to maintain the activated clotting time at >300 seconds. Balloon angioplasty (BA) was performed according to standard clinical practice. After successful angioplasty, intracoronary β-irradiation was performed as previously described,[8] and repeat angiography and IVUS motorized pullback were carried out. If stenting was indicated due to a residual stenosis of >30% diameter stenosis or dissection, a stent was implanted with high-pressure postdilatation and IVUS guidance. Finally, repeat angiography and IVUS were carried out. Intracoronary nitrates were administered immediately before each of the IVUS pullbacks. At follow-up (6 to 8 months), further IVUS analysis of the treated vessel was performed. The prescribed doses were 0 Gy (14 vessels), 12 Gy (8 vessels), 14 Gy (9 vessels), 16 Gy (9 vessels), and 18 Gy (13 vessels).

IVUS Image Acquisition Analysis System

The methodology of 3-D IVUS image acquisition and quantitative analysis has been described previously.[5,9] In brief, the segment subject to 3-D reconstruction was examined with a 30-MHz single-element mechanical transducer IVUS system (ClearView, CVIS; Boston Scientific Corp). ECG-gated 3-D IVUS image acquisition and digitization were performed with a computerized workstation (EchoScan; TomTec).[10] IVUS images were acquired that coincided with the peak of the R wave, which eliminates the artifacts caused by the movement of the heart during the cardiac cycle. The IVUS transducer was withdrawn in 0.2-mm steps with an ECG-triggered pullback device.

A Microsoft Windows–based contour detection system, developed at the Thoraxcenter, was used for 3-D volumetric quantification.[11] This program constructed 2 longitudinal sections from the data set and identified the contours that correspond to the lumen, media, or stent boundaries. Volumetric data were automatically

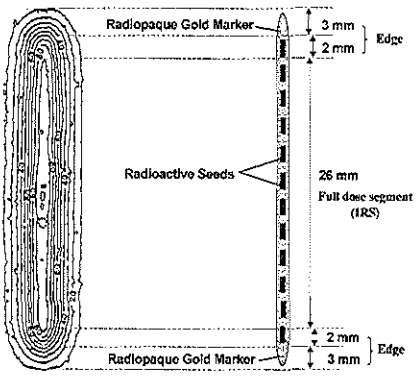

Figure 1. Isodose rate contour map and radiation source train. Left, Isodose rate contour map at a depth of 1.89 mm (10 mGy/s contour intervals) as described by The National Institute of Standards and Technology. This depth (1.89 mm) illustrates an isodose model to resemble radius of coronary artery wall. Longitudinal dose fall-off may be extrapolated from this graphic. Right, Radiation source train. Central part of source train (26 mm) receives approximately full dose.

calculated with the following formula: $V=\Sigma^{n}_{i=1} A_i \times H$, where V is volume; A is the area of external elastic membrane, lumen, or plaque in a given cross-sectional ultrasound image; H is slice thickness of the cross section (0.2 mm); and n is the number of digitized cross-sectional images that encompass the volume to be measured.[11] Offline analyses were performed by 3 independent experienced analysts (K.K., M.C., M.S.) who checked and edited all of the contours of the planar images. The accuracy of this method has been validated in vitro (phantom) and in vivo.[12] Intraobserver and interobserver variabilities of this system have also been determined in clinical protocols.[9] Intraobserver variability assessed with analysis of the IVUS volumetric studies at intervals of ≥3 months has been reported: −0.4±1.1% in lumen volume, −0.4±0.6% in total vessel volume, and −0.3±1.0% in plaque volume with ECG-gated motorized pullback.

The methodology to define the treated segment in the irradiated patients has been previously described.[5] An angiogram was performed during contrast injection after positioning of the delivery catheter, and the relation between anatomic landmarks and the 2 radiopaque markers of the radiation source was noted. Typically, the aorto-ostial junction, side branches, stent, or a combination were used as landmarks. During the subsequent IVUS imaging pullback, this reference point was recognized and used for selection of the 30-mm-long segment where the radiation source train was placed and both 3-mm distal and proximal edges (36-mm-long segment in total). At follow-up, correct matching of the region of interest was performed by comparing the longitudinal reconstruction with that after the procedure. The longitudinal distance of the 100% isodose is ≈26 mm, as illustrated in Figure 1. Thus, we defined the target irradiated segments (IRS) as the segments covered by the 26-mm full-activity central portion of the radiation source train and the edges of the IRS as the adjacent (distal and proximal) 5-mm coronary segments, which consisted of 2 mm inside the gold markers and 3 mm proximal or distal including the gold markers (Figure 1). IRS-containing stents (n=12) were excluded from the analysis.

The 5-mm edge segments selected in our study received low-dose radiation because β-emitting $^{90}Sr/^{90}Y$ source has an acute fall-off of delivery dose related to the distance.[13,14] For instance, the highest prescribed dose in our study was 18 Gy, and the calculated longitudinal dose per millimeter from the 100% isodose boundary is expected to be 15.5±1.0 Gy at 1 mm, 11.0±1.0 Gy at 2 mm, 5.5±0.5 Gy at 3 mm, 2.4±1.0 Gy at 4 mm, and <1 Gy at 5 mm.

To select the noninjured segments, all locations of deflated balloons, stent delivery system, inflated balloons, and radiation

source train were recorded in the angiogram. The deflated balloon, stent delivery system, and delivery radiation catheter were also filmed during contrast injection. All angioplasty balloons used in this study had 2 radiopaque markers in both extremities. Each cine frame of angiograms that show the position of inflated balloon, deflated balloon markers, stent delivery system, and the radiation source train can be displayed simultaneously on the separated screen during offline analysis with the Rubo DICOM Viewer (Rubo Medical Imaging). A continuous ECG recording was also displayed, which permitted the selection of images in the same moment of the cardiac cycle. By identifying the relationship between landmarks and device radiopaque markers, we were able to select only the balloon- or stent-injured fully irradiated coronary segment (covered by the 26-mm central portion of the radioactive source train). Therefore, all of the injured edge segments were excluded. At follow-up, it was also possible to determine the noninjured edge segments according to the same method, because all of the follow-up cine films were taken in the same views as before and after the procedure. This angiographic analysis was performed independently by 2 cardiologists (K.K., M.C.). Only the edges, which both investigators regarded as noninjured segments, were finally considered to be noninjured edges. There was only 10% disagreement in the definition of injured irradiated edge segment with this methodology. The 3-mm stent edges were also considered to be injured segments, because the balloon of the stent delivery system may protrude ≈2 to 3 mm outside the stent.

Quantitative 3-D IVUS Analysis

Total vessel volume (TVV) determined with external elastic membrane boundaries and lumen volume (LV) were measured. Plaque volume (PV) was automatically calculated by subtracting LV from TVV. To assess the volumetric changes of the vessel structures after 6 to 8 months, the Δ value for each measurement was calculated (Δ=follow-up−postprocedure). To eliminate the influence of the vessel size and the length of the analyzed segment, which affects volume calculations, percent Δ change (Δ volume/postprocedure volume) was also calculated.

"Remodeling" was defined as a continuous process that involved any positive or negative changes in TVV.[15] In the present study, remodeling of the vessel wall was considered when TVV increased or decreased compared with postprocedure measurements by ≥2 SDs (±1.3%) of the intraobserver variability. By using this technique, the potential intrinsic error of the method may be avoided.[16,17]

Statistical Analysis

Quantitative data are presented as mean±SD. Comparisons between postprocedure and follow-up IVUS parameters were compared by paired Student's *t* test. Comparisons of the IVUS data among the 3 groups (noninjured edge of the irradiated vessels, IRS, and noninjured edge of the placebo group) were performed by 1-way ANOVA. Bonferroni's test was applied for comparison between groups. The difference between proximal and distal edges was compared by 2-tailed Student's *t* test. The correlation between percent change in plaque volume and prescribed dose, corrected by the mean total vessel area at the edges based on 3-D IVUS measurement, were tested by Pearson's correlation. A value of $P<0.05$ was considered statistically significant.

Results

Baseline clinical, demographic, and angiographic characteristics were similar between irradiated and placebo patients (Table 1). No myocardial infarction or death was observed in this population during the 6- to 8-month follow-up. Target lesion revascularization was performed after follow-up angiography in 6 vessels in the irradiated group (16%) and 2 vessels in placebo group (14%). The noninjured edges were not involved in any of the restenotic lesions that required further intervention in both groups.

TABLE 1. Clinical and Lesion Characteristics

	Irradiated Group (n=36)	Placebo Group (n=14)	*P*
Clinical			
Age, y	57±9	57±9	NS
Male, n (%)	27 (75)	13 (93)	NS
Coronary risk, n (%)			
Smoking history	26 (72)	11 (79)	NS
Dyslipidemia	21 (58)	7 (50)	NS
Diabetes mellitus	4 (11)	2 (14)	NS
Hypertension	14 (39)	2 (14)	NS
Family history	17 (47)	7 (50)	NS
Unstabele angina, n (%)	13 (36)	5 (36)	NS
Multivessel disease, n (%)	12 (33)	1 (7)	NS
Lesions			
Treated lesions, n	39	14	
Vessel location, n (%)			
LAD	15 (38)	6 (43)	
LCx	10 (26)	3 (21)	NS
RCA	14 (36)	5 (36)	
Stent implantation	12 (31)	7 (39)	NS
Maximum balloon size, mm	3.63±0.6	3.63±0.5	NS

LAD indicates left anterior descending coronary artery; LCx, left circumflex coronary artery; and RCA, right coronary artery.

Forty-eight edge segments (20 distal and 28 proximal edges) and 27 irradiated segments without stents were analyzed with 3-D volumetric IVUS in the irradiated population. Thirty edges were excluded from this analysis. The reasons for exclusion were ostial location of the proximal end of the source (n=11), overlapping of 1 of the edges with large side branches (>2.0-mm diameter) (n=5) or stent (n=6), injury of 1 of the edges by angioplasty balloon (n=4), and lack of follow-up IVUS analysis with the ECG-gated motorized pullback (n=4).

In the placebo group, 18 edges (11 distal and 7 proximal edges) were examined with 3-D volumetric IVUS. Ten edges were excluded because of ostial location of the proximal end of the dummy source (n=6), overlapping of 1 of the edges with large side branches (n=1), and injury of 1 of the edges (n=3).

All 3-D IVUS volumetric measurements of PV, TVV, and LV are listed in Table 2. Some degree of atherosclerosis (≥15% plaque burden) was observed in most of the noninjured edges in the postprocedure IVUS analysis, but no edge (radiation or placebo group) had >50% plaque burden. Compared with the postprocedure measurement, there was a significant increase in PV in the noninjured edges of the irradiated vessels (ΔPV=4 mm^3) at follow-up. Because TVV on average decreased by −2 mm^3 (P=NS), LV decreased at follow-up in the noninjured edge of the irradiated vessels (ΔLV=−6 mm^3). In the placebo group, there also was a tendency of plaque increase at follow-up (ΔPV=4 mm^3) in the noninjured edge of the placebo group (P=0.06).

TABLE 2. Volumetric Measurement of 3-D IVUS

	IRS (n=27)		Noninjured Edge Irradiated Vessel (n=48)		Noninjured Edge Placebo (n=18)	
	Post	Follow-Up	Post	Follow-Up	Post	Follow-Up
PV, mm^3	196±56	234±69*	32±15	36±16*	27±14	31±15†
TVV, mm^3	441±136	480±159‡	81±32	79±31	65±21	67±24
LV, mm^3	245±101	247±114	48±22	42±21§	38±15	37±16

*P<0.001, †P=0.06, ‡P=0.004, §P=0.001.
Post indicates post procedure.

Comparisons among the geometric changes of the 3 groups (IRS, noninjured edges of the irradiated vessels, and noninjured edges of the placebo group) are demonstrated in Figure 2. The percent increase in PV was similar among IRS, noninjured edges of the irradiated vessels, and those of placebo group (+21.0% versus +19.6% versus +21.5%, respectively). TVV increased in IRS significantly among the 3 groups (+9.4% at IRS; −1.0% at noninjured edges of the irradiated vessels; +3.8% at noninjured edge of the placebo, P=0.021). The difference was observed only between IRS and noninjured edges of the irradiated vessels by post hoc test (P=0.017). Percent changes in LV were different (+1.7% versus −10.0% versus −2.5%, respectively, P=0.049) among the 3 groups. LV tended to decrease in the noninjured edges of irradiated patients compared with IRS (P=0.053).

Comparisons between the geometric changes of the proximal and distal noninjured edges are shown in Figure 3. Although there was no statistical difference in geometric change between distal and proximal edges, the percent increase in PV tended to be greater in the proximal edges than in the distal edges (+27.0% versus +9.2%).

Finally, there was no correlation between the percent increase in PV and prescribed dose corrected by mean vessel area at the edges (P=0.76, r=−0.046).

Discussion

This is the first study to investigate the geometric changes of noninjured margins of endovascular catheter–based radiation therapy. The edge effect, a decrease in lumen volume at follow-up, was observed in the noninjured edges of the irradiated vessels (Table 2). However, plaque proliferation induced by low-dose radiation may not fully account for the occurrence of this phenomenon, because plaque volume increased similarly in the noninjured edges of placebo group (Figure 2).

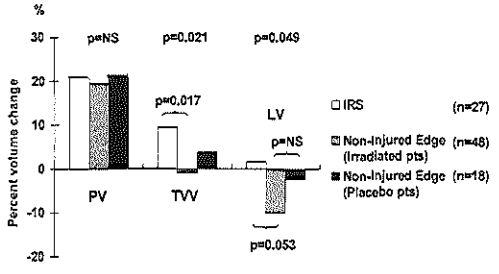

Figure 2. Comparisons of percent volume changes among IRS and noninjured edges of both irradiated and placebo patients.

Lumen loss was observed in the noninjured edges of the irradiated group. The decrease in LV observed in these edges was mainly due to the lack of positive vessel remodeling (ie, no remodeling)[15] to accommodate the plaque increase, which occurred similarly in all analyzed segments. Likewise, the lumen also decreased (2.5%) in the noninjured edges of the control group, but in this case we observed some degree of vessel enlargement (3.8% increase in TVV). The facilitation of favorable positive remodeling[15] promoted by radiation may explain the preservation of lumen dimension (1.7% increase in LV) observed only in the IRS. Both phenomena, positive remodeling stimulated by intravascular radiation after balloon angioplasty and different patterns of vascular remodeling (positive, negative, or no remodeling) in nonirradiated coronary segments, have been reported previously.[5,18–20]

Although the stimulatory effect of low-dose radiation on plaque proliferation has been demonstrated in injured animal arteries,[6,7] no enhanced plaque growth was observed in the noninjured edges compared with placebo. Plausible explanations for the PV increase in the noninjured edges of both irradiated and placebo groups would be the nonmeasurable vessel injuries caused by the guiding catheter (ie, deep engagement) during the procedure or the devices that cross coronary segments (guidewires, stents, balloons, IVUS catheter, and the 5F radiation delivery catheter). Indeed, a tendency of greater plaque increase was observed in the proximal edges, where these types of injury may occur more frequently, although it might have been hypothesized that the 5F radiation delivery catheter could induce higher injury to the distal part due to the tapering of the vessel.

It is nevertheless important to emphasize that this phenomenon occurred in segments not injured by balloon inflation, which may highlight the importance of the use of a less aggressive approach: the avoidance of deep catheter engagement, guidewire entrapment, or rough device introduction against resistance, especially in tortuous vessels. To avoid device-induced injury, low-profile and more flexible radiation delivery catheters will be a worthy development for catheter-based brachytherapy.

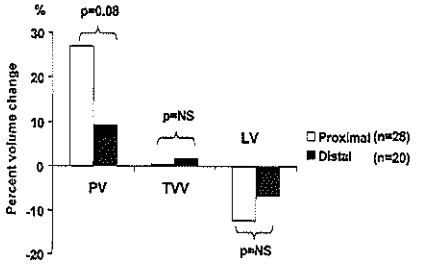

Figure 3. Comparisons of percent volume changes between proximal and distal edges in irradiated vessels.

The 10% lumen loss observed in the edges of the irradiated vessels had no clinical impact, because no repeat revascularization was performed due to noninjured edge stenosis. However, this finding may have important implications if plaque grows locally (ie, 1- or 2-mm short segment) or lumen reduction occurs in small or diffuse diseased vessels in the general treated population.

In conclusion, the edge effect occurs after catheter-based β-irradiation in the margins that were not injured by balloon inflation. This phenomenon was basically due to plaque growth without vessel remodeling. Our findings suggest that low-dose radiation may not be implicated as the cause of the edge effect and that clinically nonassessable device injury would be considered as a plausible explanation for this phenomenon. Clinically, the edge effect observed in our midterm follow-up IVUS study did not represent a drawback of the catheter-based intracoronary β-radiation.

Study Limitations

The number of the placebo patients was relatively small. However, the use of the "state-of-the art" 3-D IVUS technology in our study may overcome this limitation, because a smaller number of patients are necessary to demonstrate statistical differences in studies with volumetric IVUS parameters.[21]

Minor inaccuracy in the selection of the segments of interest cannot be completely ruled out, although the methodology applied in the present study was the most appropriate at this time. Ideally, intervention devices that incorporate IVUS imaging elements would be the solution for this drawback.

In a human clinical study, it is not possible to quantify the degree of vessel injury (ie, injury score),[22] which would provide further insight about this issue.

The actual dose received at irradiated and edge segments may have some implications in the geometric changes of the edges and would be interpreted as a limitation of our investigation. However, the study was not aimed at establishing a threshold of dose to be delivered to the irradiated target site, because an adjacent coronary segment will invariably receive low dose of radiation.

The 6- to 8-month follow-up period of this study may be too short to demonstrate the long-term arterial response to the radiation treatment. Increased risk of accelerated atherosclerosis progression after radiation therapy for malignancy has been reported.[23–27] Further, a recent report has shown that continuous low-dose rate irradiation delivered by radioactive stent promotes "atheromatous" neointimal formation.[28] Therefore, a question still remains to be elucidated: Does endovascular radiation have any influence on the progression of atherosclerosis, especially in the adjacent nontarget irradiated segments?

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Chapter 5

Relationship between Tensile Stress and Plaque Growth after Balloon Angioplasty Treated with and without Intracoronary ß-Brachytherapy

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Relationship between tensile stress and plaque growth after balloon angioplasty treated with and without intracoronary beta-brachytherapy

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Aims We investigated the influence of tensile stress on plaque growth after balloon angioplasty with and without beta-radiation therapy.

Methods and Results Thirty-one consecutive patients successfully treated with balloon angioplasty were analysed qualitatively and quantitatively by means of an ECG-gated three-dimensional intravascular ultrasound post-procedure and at follow-up. Eighteen patients were irradiated with catheter-based beta-radiation ($^{90}Sr/^{90}Y$ source) and 13 were not (control). Studied segments were divided into 2 mm subsegments. Thus 184 irradiated and 111 non-irradiated subsegments were included. Tensile stress was calculated according to Laplace's law. The radiation dose was calculated by means of dose–volume histograms. Plaque growth was positively correlated to tensile stress in both the radiation and control groups ($r=0{\cdot}374$, $P=0{\cdot}0001$ and $r=0{\cdot}305$, $P=0{\cdot}001$). Low-dose subsegments (<6 Gy) had a significant correlation ($r=0{\cdot}410$, $P=0{\cdot}0001$) whereas no correlation was observed in the effective-dose subsegments (≥6 Gy). Multivariate analysis identified tensile stress as the only independent predictor of plaque increase in non-irradiated subsegments, whereas actual dose and plaque morphology were stronger predictors in irradiated subsegments.

Conclusion The results of this study suggest that plaque growth is related to tensile stress after balloon angioplasty. Intracoronary brachytherapy may alter the biophysical process on plaque growth when the prescribed dose is effectively delivered.

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Key Words: Tensile stress, balloon angioplasty, intracoronary radiation, intravascular ultrasound, plaque growth, dose–volume histogram.

See page 1994 for the Editorial comment on this article

Introduction

Intracoronary brachytherapy is a novel technique to prevent restenosis after percutaneous coronary intervention. A significant reduction in re-restenosis after intravascular radiation therapy of in-stent restenosis has been reported recently[1]. In addition, this mode of therapy has been applied in the treatment of de novo coronary lesions[2–4], since experimental and clinical work has shown that radiation favourably affects both vascular remodelling and neointimal proliferation after angioplasty[5–9].

Mechanical stimuli, such as the force exerted by blood pressure on the vessel wall, may evoke various signal transductions (i.e. calcium/natrium ion channels, renin–angiotensin systems, integrins) in vascular smooth muscle cells and to stimulate extracellular matrix formation[10,11]. Accordingly, tensile stress, together with shear stress, may contribute to atherosclerosis[12,13]. The clinical confirmation of these hypotheses requires laborious and sophisticated methodology[14] and has yet to be investigated. Furthermore, whether these biophysical factors still influence neointimal formation after balloon injury when coronary vessels are treated with

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intracoronary radiation, a therapy suggested to inhibit neointimal formation in a dose-dependent manner[15,16], remains to be determined.

We endeavoured to investigate the influence of tensile stress on plaque growth after balloon angioplasty in a population treated with beta-radiation therapy using 3-D intravascular ultrasound volumetric analysis.

Method

Population

Thirty-one consecutive patients successfully treated with balloon angioplasty were enrolled in this study. Eighteen patients underwent catheter-based intracoronary beta-radiation therapy using the Beta-Cath System® (Novoste Corp), 13 patients (the control group) were treated with conventional balloon angioplasty without radiation during the same period. The irradiated patients were randomly assigned to three different prescribed doses (12, 14 and 16 Gy) 2 mm from the axis of the source. The radiation source train consists of a series of 12 independent 2·5 mm long cylindrical seeds, which contain the radioisotope $^{90}Sr/^{90}Y$ sources, and are bordered by two gold radioopaque markers, distal and proximal, separated by 30 mm.

Inclusion criteria were age 18 to 80 years; evidence of ischaemia; reference diameter of 2·5 to 3·5 mm; lesion length <20 mm; single vessel disease; de novo lesion. Patients treated with any other percutaneous device (i.e. cutting balloon, directional coronary atherectomy, rotational atherectomy, laser ablation, or stents) or those taking any specific medication under investigation were not included. Only patients with scheduled or completed 6-month angiographic and intravascular ultrasound follow-up were included in the analysis.

Intravascular ultrasound image acquisition

The coronary segment subject to 3-D reconstruction was examined with a mechanical intravascular ultrasound system (CVIS, Boston Scientific Corporation, Maple Grove, MN, U.S.A.) with a sheath-based intravascular ultrasound catheter, incorporating a 30 MHz single-element transducer rotating at 1800 rpm. ECG-gated image acquisition and digitization was performed by a workstation designed for the 3-D reconstruction of echocardiographic images (EchoScan, Tomtec, Munich, Germany). A description of this system has been reported in detail elsewhere[17–19]. In brief, the steering logic of the workstation was heart rate variability and acquired images from cycles meeting a pre-determined range of periods and coinciding with the peak of the R wave.

The methodology to define the segment of interest to be analysed has also been described previously[8,22,23]. An angiogram was performed with contrast injection after positioning the radiation delivery catheter and a deflated balloon at the site of the procedure. By the use of the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands), each angiographic sequence showing the radiation delivery catheter or the deflated balloon during contrast injection were displayed on the screen with simultaneous ECG tracing. By selecting frames at the same part of the cardiac cycle, we were able to define the location of the radiation source train, balloon inflations and their relationship with anatomical landmarks. Typically, the aorto-ostial junction and/or side-branches were used as landmarks. The anatomical landmark closest to either of the balloon markers was used as a reference point. During the subsequent intravascular ultrasound imaging, this reference point was recognized and used for selecting the area of interest: a 30 mm long segment irradiated by the radioactive source train or the balloon injured segment. At follow-up, correct matching of the region of interest was assured by both the use of the same intravascular ultrasound motorized pull-back system and comparison of longitudinal image reconstruction with that post-procedure. In the radiation group, a 26 mm segment was selected by excluding both 2 mm ends of the 30 mm whole segments between the two gold markers; this radiation source had undergone an acute dose fall-off. In the control group, segments up to 26 mm long were selected in the same manner and treated by balloon.

Intravascular ultrasound quantitative analysis

A Microsoft Windows®-based contour detection program, developed at the Thoraxcenter, was used for off-line volumetric quantification[20]. Briefly, this program constructed longitudinal sections from the data set and identified the contours corresponding to the lumen and media boundaries. Volumetric data were calculated by the formula: $V=\Sigma^{n}_{i=1} A_i * H$, where V=volume, A=area of external elastic membrane, lumen, or plaque in a given cross-sectional ultrasound image, H=thickness of the coronary artery slice reported in this digitized cross-section, and n=the number of digitized cross-sectional images encompassing the volume to be measured. Checking and editing of the contours of the planar images were performed by two independent experienced analysts. Intra-observer variability assessed by analysing intravascular ultrasound volumetric studies at least 3 months apart has been reported: $-0{\cdot}4 \pm 1{\cdot}1\%$ in lumen volume, $-0{\cdot}4 \pm 0{\cdot}6\%$ in external elastic membrane volume and $-0{\cdot}3 \pm 1{\cdot}0\%$ in plaque volumes using motorized ECG-gated pullback[19]. The application of this system has been reported in clinical studies[8,9,21,22].

Coronary segments were divided into 2 mm long subsegments (each of them presenting 10 cross-sections — 0·2 mm/slice)[9]. The independence of each subsegment is assured by the use of an ECG-gated pullback device (0·2 mm/step)[18,24].

Lumen, plaque and total vessel (external elastic membrane) volumes were quantified in each subsegment. Change (deltas) in plaque volume was calculated as follow-up minus post-procedure plaque volume.

Intravascular ultrasound qualitative analysis

All individual cross-sections were analysed qualitatively by two independent investigators blinded to the volumetric results. Thus, the type of plaque was defined in every cross-section, as intimal thickening, soft, fibrous, mixed (soft–fibrous, soft–calcific and fibrous–calcific) and diffuse calcified as proposed by Di Mario *et al.*[25]. Each subsegment was categorized as normal (<0·3 mm intimal thickening), soft, hard (fibrous and mixed) or diffuse calcified, when at least 80% of the cross-sections within the subsegments were of the same type, as described previously[9]. In those cross-sections, which contained a calcium arc up to 90°, the contour of the external elastic membrane was interpolated from the contours of the slice immediately proximal and distal to the cross-section in question. Subsegments with side-branches involving >90° of the circumferential arc in more than 50% of the cross-sections or those categorized as diffuse calcified were excluded from the quantitative analysis. Dissection was defined as a tear parallel to the vessel wall in the intravascular ultrasound images[25]; a plaque-free vessel wall was characterized by local wall thickness <0·5 mm[26] occupying <180° of the cross-section. These qualitative data should also meet the 80% criteria which characterize a subsegment.

Tensile stress

Tensile stress was calculated from the law of Laplace: TS=P * r/d, where P was the distending pressure (mean blood pressure), r the lumen radius and d the wall thickness as described previously[27]. Blood pressure was obtained from the arterial line after the introduction of the sheath and before administration of any vasodilating agent. Lumen radius was automatically calculated from cross-sectional areas[21] using the formula, $radius_{mean}=\sqrt{area/\pi}$ in each cross-section, assuming a circular model. Mean wall thickness was calculated from the difference in the local radius between the total vessel and the lumen.

Dose calculation

The actual dose received by each subsegment of the target vessel was calculated by means of dose–volume histograms[28]. This method is based on volumetric quantitative three-dimensional intravascular ultrasound. The distances between the centre of the catheter and both the lumen–intima and media–adventitia interfaces were calculated in 24 pie-slices (15°) in all cross-sections corresponding to the irradiated area (30 mm length of the source train). The prescribed dose and the accurate geometric data obtained from three-dimensional intravascular ultrasound with ECG-gated motorized pullback, enabled the cumulative curve of the dose–volume histogram for a pre-defined volume (i.e. adventitia) to be obtained. From this curve, the minimum dose received by 90% of the adventitia volume ($DV_{90}Adv$) was calculated. The methodology and feasibility of this dosimetry approach to vascular brachytherapy has been reported previously[29].

In order to investigate the influence of radiation dose on plaque growth and its interaction with tensile stress, we categorized irradiated subsegments into a low dose group ($DV_{90}Adv$ <6 Gy) and an effective dose group ($DV_{90}Adv$ ≥6 Gy). This cut-off point was based on previous observations from our group and others[9,30], that have shown that plaque growth was inhibited when at least 6–8 Gy was delivered at the adventitia.

Table 1 Baseline characteristics. Values were non-significant

Variable	Radiation group (n=18)	Control group (n=13)
Age, years	57·3 ± 9·9	59·7 ± 8·7
Gender, male	14 (78%)	13 (100%)
Hypertension	8 (44%)	4 (31%)
Diabetes	2 (11%)	2 (15%)
Dyslipidaemia	11 (61%)	7 (54%)
Family history	9 (50%)	7 (54%)
Smoking history	12 (67%)	8 (62%)
Previous MI	1 (6%)	5 (39%)
Angina status, CCS 3/4	10 (56%)	10 (77%)
Target lesion site		
LAD	8 (44%)	5 (48%)
RCA	4 (22%)	4 (31%)
LCX	6 (33%)	4 (31%)

MI=myocardial infarction; CCS=Canadian Cardiovascular Society angina class; LAD=left anterior descending coronary artery; RCA=right coronary artery; LCX=left circumflex coronary artery.

Table 2 Intravascular ultrasound quantitative and qualitative data

Variables	Radiation group	Control group	*P* value
No. of subsegments	184	111	
Baseline TVV (mm^3)	32·0 ± 9·1	30·3 ± 11·9	ns
Baseline PV (mm^3)	15·0 ± 6·1	14·1 ± 6·3	ns
Plaque morphology			
Intimal thickening	22 (12%)	26 (23%)	
Soft	49 (27%)	39 (35%)	0·002
Hard	113 (61%)	46 (41%)	
Dissection	55 (29%)	35 (32%)	ns
Plaque-free wall site	121 (66%)	58 (52%)	0·027
$DV_{90}adv$	5·37 ± 2·48	0	

TVV=total vessel volume; PV=plaque volume; $DV_{90}adv$=the minimum dose received by 90% of the adventitia volume.

Table 3 Comparison of variables among low dose, effective dose and control groups

Variables	Effective dose	Low dose	Control	*P* value
No. of subsegments	74	110	111	
Baseline				
radius (mm)	1·37 ± 0·4	1·76 ± 0·7	1·55 ± 0·8	0·001
wall thickness (mm)	1·27 ± 0·5	1·25 ± 0·4	1·20 ± 0·5	ns
mean pressure (mmHg)	97·2 ± 17·7	100·2 ± 14·2	92·6 ± 15·2	0·002
Tensile stress (kN/m^2)				
Baseline	18·3 ± 13·4	24·3 ± 18·0	20·3 ± 11·7	0·011
Follow-up	18·4 ± 10·1	17·9 ± 10·9	18·0 ± 10·6	ns

Statistical analysis

Data are presented as mean ± SD. Differences in quantitative intravascular ultrasound data among three groups (non-irradiated, low-dose, effective dose) were assessed by one-way analysis of variance (ANOVA). Comparisons between two groups were performed by the use of unpaired Student's t-test. Univariate and multivariate linear regression analyses were performed to determine the relationship between tensile stress and plaque growth and to examine the influence of other local factors; intravascular ultrasound-derived (types of tissue, presence of dissection and plaque-free wall site, and total vessel volume post-treatment) and dosimetric variables ($DV_{90}Adv$). Tensile stress was expressed as a logarithm in order to be ranged properly. All tests except the post-hoc test were two-tailed and a *P* value <0·05 was considered statistically significant. The Bonferroni correction was applied for comparison between each group when three groups were compared.

Results

Baseline characteristics

Two hundred and thirty four subsegments were defined in 18 patients in the radiation group and 130 subsegments were analysed in 13 patients in the control group. Fifty subsegments in the radiation group and 19 subsegments in the control group were excluded from the final analysis due to either ostial location (n=8), diffuse calcified plaque which precluded the quantification of the total vessel volume (n=30) or side branches involving >90° of the circumferential arc in more than 50% of the cross-sections (n=31). Therefore, 184 irradiated subsegments and 111 control subsegments were the subject of the study. Baseline characteristics are demonstrated in Table 1. There was no difference between the groups.

Intravascular ultrasound data — volumetric analysis and qualitative data

Baseline intravascular ultrasound data are presented in Tables 2 and 3. Irradiated subsegments have harder plaque and a higher incidence of plaque-free wall sites (Table 2). When the irradiated group is divided into two, those receiving the low-dose and those receiving the effective dose, low-dose subsegments have a higher radius and arterial pressure than effective dose and non-irradiated subsegments. Therefore subsegments receiving low-dose radiation have higher tensile stress at baseline (Table 3).

Plaque increased in both the irradiated and non-irradiated groups (3·1 ± 6·4 mm^3 vs 1·9 ± 4·3 mm^3, *P*=ns, respectively). However, subsegments receiving <6 Gy (n=110) at the adventitia had a significantly higher plaque increase compared to effective dose (≥6 Gy, n=74) and non-irradiated subsegments (n=111) (Fig. 1).

Influence of tensile stress on plaque growth

An example of subsegment analysis with intravascular ultrasound parameters and tensile stress is demonstrated in Fig. 2. In both the radiation and control groups, changes in PV were positively correlated with tensile stress as shown in Fig. 3. When dividing the irradiated group into low and effective doses, a similar correlation between tensile stress and plaque increase was observed in the subsegments receiving a low dose of radiation, but

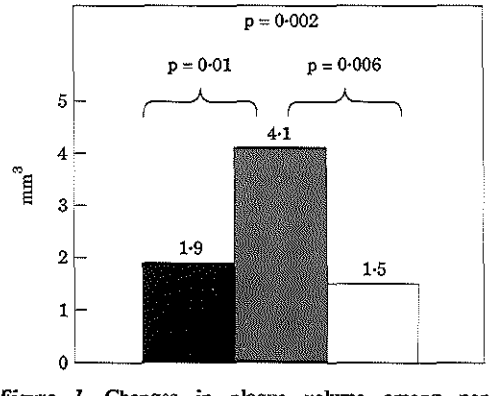

Figure 1 **Changes in plaque volume among non-irradiated (■, n=111), low-dose (▩, <6 Gy, n=110) and effective-dose (□, ≥6 Gy, n=74) subsegments.**

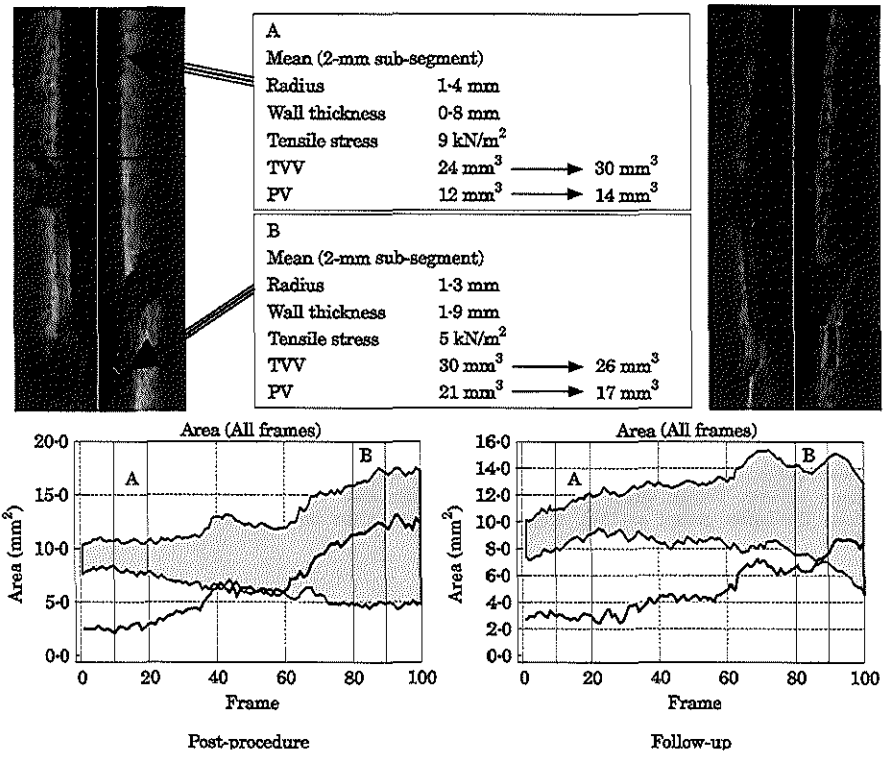

Figure 2 **An example of the results by 3-D longitudinal reconstruction of intravascular ultrasound cross-sectional images using ECG-gated pullback. Upper outside panels: Longitudinal images post-procedure (left) and follow-up (right). Upper inside panels: Parameters used in the present study (A and B). TVV=total vessel volume; PV=plaque volume. Lower panels: Charts display the subsequent volumetric quantification at post-procedure (left) and follow-up (right). The area values of the lumen (lower line) and total vessel (upper line) form the boundaries of the grey zone, which represent the plaque–media complex, and a single line depicts the absolute area value of plaque–media complex. The zones between 2 lines (A and B) correspond to the data shown in the upper inside panels.**

not in the effective dose group (Fig. 4). Although tensile stress values at baseline were different among three groups (low dose, effective dose and control), tensile stress decreased to similar values at follow-up (Table 3).

Predictors of plaque growth

Results of univariate and multivariate linear regression are shown in Table 4. Tensile stress was the only predictor of plaque growth in non-irradiated coronary subsegments in the multivariate model. However, in the irradiated group DV_{90}Adv, and plaque morphology were stronger independent predictors of plaque increase than tensile stress.

Discussion

This study demonstrates for the first time that local plaque growth is related to tensile stress after balloon angioplasty. Tensile stress was positively correlated with an increase in plaque volume in subsegments receiving low or no doses of radiation. Further, this biophysical parameter was the only independent predictor of plaque increase in the non-irradiated subsegments. However, the influence of tensile stress on plaque formation was blunted by the effective dose of radiation (Fig. 4).

Under physiological conditions and in experimental atherosclerosis, local tensile stress, which is dependent on lumen radius and wall thickness, has been suggested to stimulate atherosclerotic plaque formation[12,13,31,32]. The results of the present investigation suggest that tensile stress represents an adaptive factor in the restoration of wall stress by stimulating plaque growth[12,13,33] after balloon angioplasty, when plaque is disrupted and the balance between lumen size and wall size is lost. This hypothesis may be supported by previous experimental observations showing that: (1) tensile forces induce signal transduction in smooth muscle cells[10], although the mechanoreceptor is still unknown; (2) mechanical strain promotes smooth muscle cell growth, when these

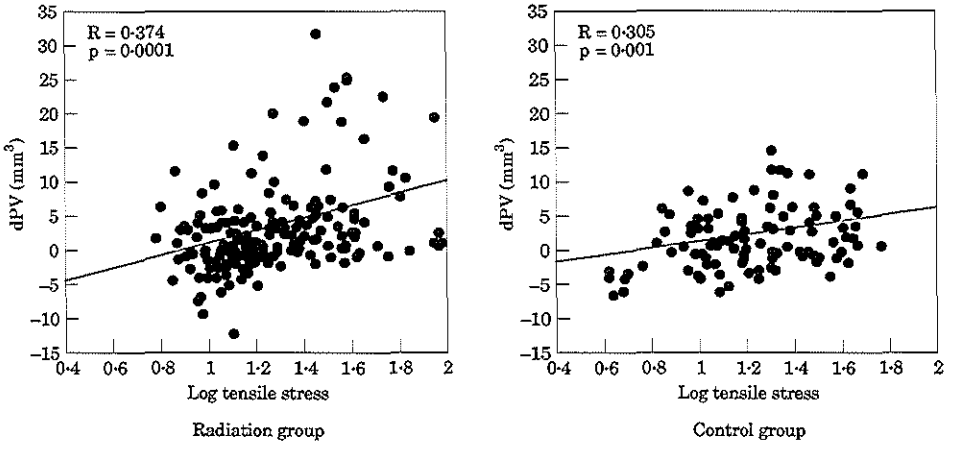

Figure 3 **Correlation between the change in plaque volume and tensile stress in all the subsegments. dPV=change in plaque volume. Tensile stress is expressed as a logarithm. Left: Correlation in all the irradiated subsegments (radiation group, n=184). Right: Correlation in the non-irradiated subsegments (control group, n=111).**

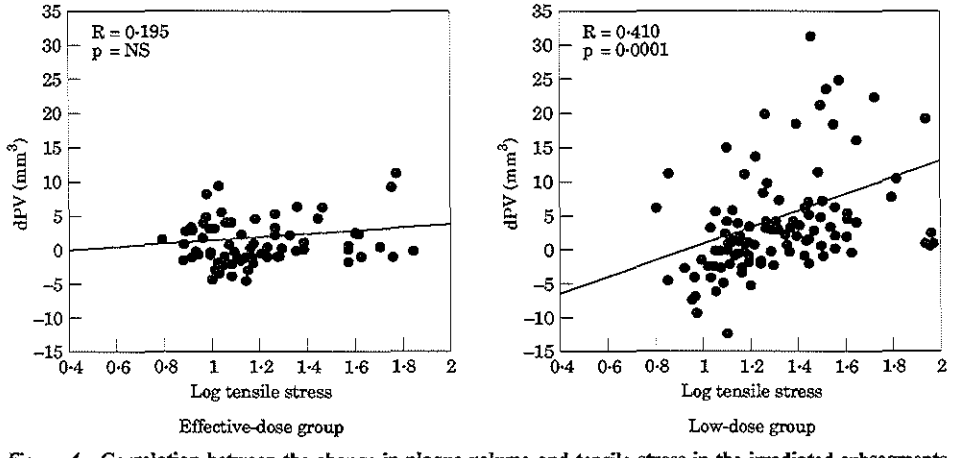

Figure 4 **Correlation between the change in plaque volume and tensile stress in the irradiated subsegments. dPV=change in plaque volume. Tensile stress is expressed as a logarithm. Left: Correlation in the effective-dose (≥6 Gy) subsegments (n=74). Right: Correlation in the low-dose (<6 Gy) subsegments (n=110).**

cells are in the proliferative phenotype (i.e. after balloon injury)[11,34]; (3) wall tension may stimulate mRNA expression of matrix metalloproteinase in human coronary arteries[35,36].

Another observation of the present study was that the influence of tensile stress on plaque volume change was abolished in subsegments receiving effective doses (Dv90 ≥6 Gy) of radiation. Radiation inhibits formation of myofibroblast scar surrounding the injury site and elicits changes in intracellular molecules: DNA is considered the critical target damaged by ionizing radiation by both direct and indirect processes. These molecular changes ultimately prevent negative vascular remodelling and plaque formation in the clinical context[37]. In the multivariate model, one may observe that tensile stress, although still an important predictor of plaque proliferation, lost its power in the irradiated group. It should be taken into account that more than half of the subsegments (n=110) received lower than the effective dose of radiation and that tensile stress was not a predictor of plaque increase when only effectively irradiated subsegments were considered. These findings may be explained by the potential modification of the arterial wall mechanoreceptors responses by radiation. This speculative explanation requires further investigation.

Table 4 Univariate and multivariate analysis for the predictors of plaque growth

Variables	Radiation group				Control group			
	Univariate	Multivariate			Univariate	Multivariate		
	P	Beta	*P*	95% CI	*P*	Beta	*P*	95% CI
Constant		7·43	ns	4·38/10·49		0·05	ns	−1·51/1·61
Plaque hard	0·0001	−3·62	0·0001	−5·46/−1·78	ns		ns	
Dissection	0·0001		ns		ns		ns	
Thin wall site	ns				ns			
Total vessel volume	ns				ns			
Tensile stress	0·0001	0·06	0·038	0·003/0·115	0·007	0·09	0·007	0·03/0·16
DV_{90}adv	0·0001	−0·64	0·0001	−0·98/−0·29	N/A			

The type of plaque characterized by intravascular ultrasound was also negatively correlated with increase in plaque volume (Table 4). Tissue characterization by intravascular ultrasound, as defined in the present study, has been shown to have a high histopathological correlation[38,39]. The diminished lipid contents and lower cellularity characteristics of mature plaques (fibrous or calcified lesions) may explain the diminished proliferative response of hard plaques as characterized by intravascular ultrasound[40].

The findings that subsegments receiving <6 Gy had a higher plaque increase than non-irradiated subsegments are in accordance with recent clinical and experimental reports showing the somewhat paradoxical induction of plaque formation by low-dose radiation[23,41,42]. The higher value of baseline tensile stress in the low-dose subsegments may in itself have impacted on the higher plaque growth. However, it is nevertheless important to note that the dose of radiation was the strongest inhibitory factor of plaque growth (Table 4), which may highlight that radiation inhibits plaque proliferation in a dose-dependent manner[15,16].

Limitations

In the present study, coronary pressure was not obtained by intra-coronary sensor tip wire, but by measuring the aortic pressure through a sheath. Coronary pressure used in the present study may be inaccurate where residual pressure gradient induced by non-significant stenosis exists either proximal to the lesion or in the lesion. Also tensile stress calculation is based on the assumption that the lumen is circular. Further investigation using a finite element model and coronary pressure guide wire will be necessary to confirm the concept.

The contribution of tensile stress to the total plaque growth may be small (approximately 10%). Since restenosis is a multi-factorial process that has not been fully elucidated yet, other local factors (i.e. shear stress and inflammatory markers) may also have considerable impacts in the mechanism of restenosis.

Conclusions

The results of this study suggest that local plaque growth is related to tensile stress after balloon angioplasty. Intracoronary brachytherapy may alter this biophysical process on plaque growth when the prescribed dose is effectively delivered.

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Chapter 6

Methodological and clinical implications of the relocation of the minimal luminal diameter after intracoronary radiation therapy. Dose Finding Study Group.

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Methodological and Clinical Implications of the Relocation of the Minimal Luminal Diameter After Intracoronary Radiation Therapy

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OBJECTIVES The aims of the study were to determine the incidence of relocation of the minimal luminal diameter (MLD) after beta-radiation therapy following balloon angioplasty (BA) and to describe a new methodological approach to define the effect of brachytherapy on treated coronary stenoses.

BACKGROUND Luminal diameter of coronary lesions may increase over time following angioplasty and irradiatation. As a result, the MLD at follow-up may be relocated from its location preintervention, which may induce misleading results when a restricted definition of the target segment by quantitative coronary angiography (QCA) is performed.

METHODS Patients treated with BA followed by intracoronary brachytherapy according to the Dose-Finding Study constituted the study population. A historical cohort of patients treated with BA was used as control group. To be included in the analysis, an accurate angiographic documentation of all instrumentations during the procedure was mandatory. In the irradiated patients, four regions were defined by QCA: vessel segment (VS), target segment (TS), injured segment (INS), and irradiated segment (IRS).

RESULTS Sixty-five patients from the Dose-Finding Study and 179 control patients were included. At follow-up, MLD was relocated more often in the radiation group (78.5% vs. 26.3%; $p < 0.0001$). The rate of >50% diameter stenosis differed among the four predefined regions: 3.1% in the TS; 7.7% in the INS; 9.2% in the IRS and 13.8% in the VS.

CONCLUSIONS Relocation of the MLD is commonly demonstrated after BA and brachytherapy, and it should be taken into account during the analysis of the results of radiation clinical trials. (J Am Coll Cardiol 2000;36:1536–41) © 2000 by the American College of Cardiology

During the past 10 years the efficacy of percutaneous interventions in preventing restenosis has been assessed by the use of quantitative coronary angiography (QCA) (1–4). This technique of analysis has become the gold standard for the assessment of coronary angiograms in the context of scientific research due to its superior accuracy and objectivity as compared to visual and hand-held caliper measurements; in addition, it possesses a better inter- and intra-observer variability (5,6). Consequently, the percent diameter stenosis has become the usual output of this analysis, and the value of 50% has gained widespread acceptance to define the presence of restenosis in the treated coronary segment (7). Intravascular ultrasound (IVUS) studies demonstrated that restenosis after balloon angioplasty (BA) is mainly due to neointimal hyperplasia and vessel shrinkage at the site of the injury (8–10).

Pioneers in intracoronary radiation therapy have demonstrated that in a majority of patients the luminal diameter at the site of the treated lesion may increase during the follow-up, rather than decrease (11). Three-dimensional IVUS analysis has shown that this phenomenon is induced by positive remodeling of the vessel wall at the site of the irradiated segment (IRS) (12). As a result, the minimal luminal diameter (MLD) of coronary segments treated with brachytherapy following percutaneous interventions may be relocated at follow-up from its location pre-intervention. A restricted definition of the target segment by QCA could induce misleading results and make any comparison to previous nonradiation studies unfair. This study was intended to 1) determine the incidence of the relocation of the MLD after beta-radiation therapy following successful BA and 2) to describe a new methodological approach to analyze and report accurately the effect of brachytherapy on the treated coronary artery.

METHODS

Patient selection. Patients eligible for the study were those successfully treated with BA followed by intracoronary radiation according to the Boston Scientific/Schneider Dose-Finding Study (13). The purpose of this trial was to determine the effect of various doses of beta-irradiation on coronary artery restenosis after BA with or without stent implantation in patients with single de novo lesions of native coronary arteries. The isotope selected was the pure

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Abbreviations and Acronyms

BA = balloon angioplasty
Gy = gray
INS = injured segment
IRS = irradiated segment
IVUS = intravascular ultrasound
MLD = minimal luminal diameter
QCA = quantitative coronary angiography
TS = target segment
VS = vessel segment

beta-emitting ^{90}Y, and patients were randomized to receive doses of 9, 12, 15 or 18 gray (Gy) at 1 mm tissue depth. The delivery of radiation was carried out by the use of the Schneider-Sauerwein Intravascular Radiation System (14). In brief, this system comprises 1) a flexible coil made of titanium-coated pure yttrium affixed at the end of a thrust wire between proximal and distal tungsten markers; 2) a centering catheter, which is a segmented balloon consisting of four interconnected compartments and which allows the source lumen to be centered relative to the arterial lumen; and 3) a computerized afterloader that allows automated advancement and positioning of either the dummy or the active source (14).

QCA analysis and definitions. The QCA analysis was performed off-line by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands). All angiograms were evaluated after intracoronary administration of nitrates. Analysis was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands). Calibration of the system was based on dimensions of the catheters unfilled with contrast medium. This method of analysis has been previously validated (4,15,16). The area of interest was selected after reviewing all cinefilms performed during the index procedure. Any angiographic sequence showing the lesion preintervention, positions of angioplasty balloon and radiation source can be displayed simultaneously on the screen using the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands). The electrocardiographic (ECG) tracing is also displayed in any angiographic sequence. By selecting frames in the same part of the cardiac cycle, we were able to define the location of the radiation source and angioplasty balloon relative to the original lesion. The analyst defined a coronary segment bordered by angiographically visible side branches that encompassed the original lesion, angioplasty balloon and radiation source. This segment was defined as the "vessel segment" (VS) (Fig. 1). The MLD was determined in the VS pre-intervention by edge detection and was averaged from the two orthogonal projections. Reference diameter was automatically calculated for the VS by the interpolated method (4). The percent diameter stenosis was calculated from the MLD and the reference diameter (7).

At the time of the procedure, all angioplasty balloons, when deflated, were filmed in place with contrast injection in the same projections as were the VS. After successful BA, intracoronary brachytherapy was performed. Both the location of the centering balloon and the active wire in place

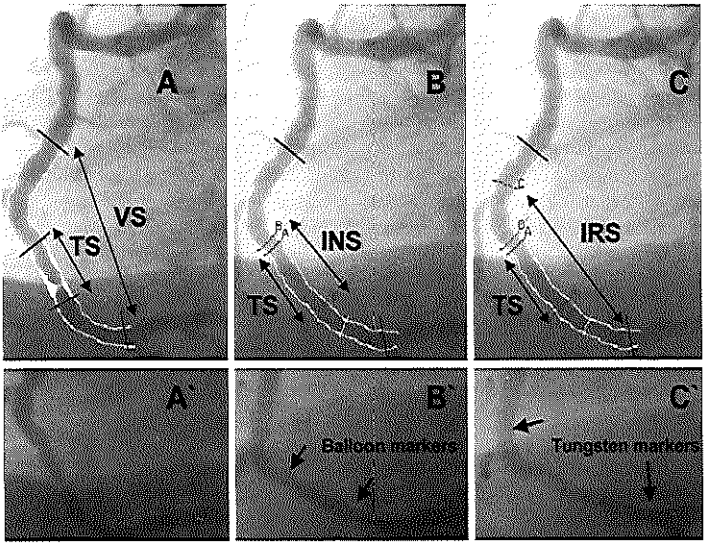

Figure 1. (A) Target segment (TS) is between proximal and distal margin of the target lesion, automatically defined by the quantitative coronary angiography system. Vessel segment (VS) is bordered by visible side branches, which encompass the target segment (TS) and the position of the angioplasty balloon and radiation source. (A') Original lesion in the middle part of the right coronary artery before intervention. (B) Injured segment (INS) is defined as the segment encompassed by the most proximal and most distal marker of the angioplasty balloon. (B') Arrows indicate the markers of the deflated angioplasty balloon filmed in place with a contrast injection. (C) The segment encompassed by the inner part of the two tungsten markers of the radiation delivery system defined as the irradiated segments (IRS). (C') Arrows indicate the inner parts of the radiation source tungsten markers filmed with a contrast injection.

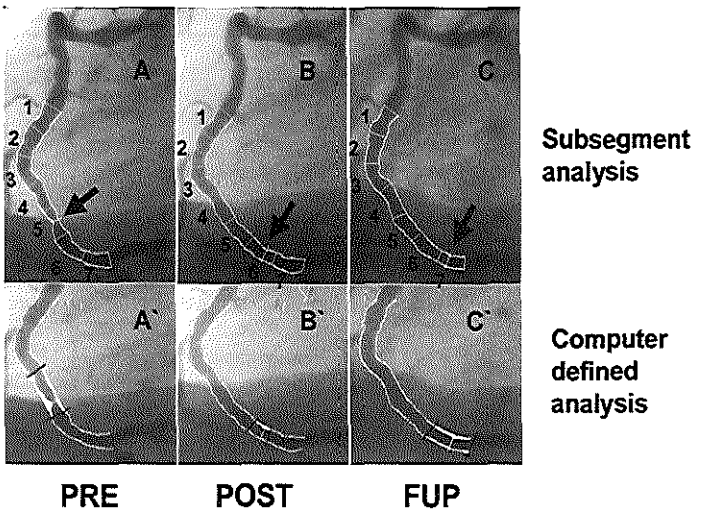

Figure 2. (A) Subsegmental analysis before procedure. Vessel segment (VS) was automatically divided into 5-mm subsegments by the CAAS II system. The original lesion is located at segment No. 5 preprocedure as the arrow indicates. (A') Computer defined analysis preprocedure. (B) Subsegmental analysis at postprocedure. Minimum lumen diameter is located at segment No. 6 (arrow). (B') Computer-defined analysis postprocedure. (C) Subsegmental analysis at follow-up. Minimum lumen diameter is located at segment No. 7 (arrow). (C') Computer-defined analysis at follow-up.

were filmed in the same projections as performed previously. The proximal side branch within the VS was used as an index anatomical landmark. The CAAS software computed distances from this proximal sidebranch to 1) the inner part of the proximal tungsten marker, 2) the proximal marker of the angioplasty balloon, 3) the proximal margin of the obstruction segment, 4) the distal margin of the obstruction segment, 5) the distal marker of the angioplasty balloon, and 6) the inner part of the distal tungsten marker. The "target segment" (TS) was encompassed by the proximal and distal margin of the obstructed segment. The segment encompassed by the most proximal and most distal marker of the angioplasty balloon defined the "injured segment" (INS). The segment encompassed by the inner part of the two tungsten markers defined the IRS (Fig. 1). All regions of interest were superimposed on the pre-, post-procedural and follow-up angiograms. "Geographical miss" was defined for those cases in which the entire length of the INS was not fully covered by the IRS (17).

Using the software of the CAAS system, the analyst is able to perform a subsegmental analysis within the VS. The segment is automatically divided into subsegments of equidistant length (on average, 5.0 ± 0.3 mm). The subsegment containing the MLD was taken as the index segment, and this enabled relocation of the MLD to be defined (Fig. 2). "Relocation pre-post" was defined as those cases in which the MLD of the VS post-treatment was located in a different subsegment in the two orthogonal projections from that of the index procedure. "Relocation post-fup" was defined as those cases in which the MLD of the VS at follow-up was located in a different subsegment in the two orthogonal projections from that of the post-procedure. "Relocation pre-fup" was defined as those cases in which the MLD of the VS at follow-up was located in a different segment in the two orthogonal projections from that of the index procedure (Fig. 2).

Additionally, the analyst computed the MLD in every region of interest and calculated the acute gain, the late loss and the frequency of >50% diameter stenosis on a regional basis. "Acute gain" was defined as MLD posttreatment minus MLD preintervention. "Late loss" was defined as MLD posttreatment minus MLD at follow-up. "Restenosis" was defined as diameter stenosis >50% at follow-up.

Control group. A historical cohort of consecutive patients treated with BA from the BENESTENT II trial (18) and presenting with matched views and correct angiographic documentation was used as the control group. The VS, TS, and relocation of the MLD were defined in this cohort as described above.

Statistical analysis. Data are presented as mean ± SD or proportions. To compare qualitative variables, the chi-square test was carried out. To compare quantitative variables, the Student *t* test was performed. All tests were two-tailed, and a value of $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics. One hundred and eighty-one patients were included in the dose-finding study. Of these, 51 patients received a stent. The remaining 130 patients treated with BA alone followed by beta-radiation were eligible for the study. By comparing the technician worksheet with the angiograms recorded, the analyst was able to identify those patients for whom all balloon inflations and source positioning were filmed and all target views matched. Using this

Table 1. Baseline Characteristics

	Dose-Finding Group (n = 65)	Control Group (n = 179)
Age (yrs)	64 ± 9	62 ± 10
Gender (male)	46 (70.7%)	137 (76.5%)
Treated artery		
Left anterior descending	28 (43.1%)	80 (44.7%)
Left circumflex	7 (10.8%)	22 (12.3%)
Right coronary	30 (46.1%)	77 (43%)
Coronary risk factors		
Systemic hypertension	35 (53.8%)	89 (49.7%)
Diabetes mellitus	12 (18.5%)	27 (15%)
Smoking	33 (66.1%)	123 (68.7%)
Hypercholesterolemia	38 (58.5%)	98 (54.7%)
Family history	23 (35.4%)	60 (33.5%)
Dose		
9 Gy	18 (27.7%)	—
12 Gy	11 (16.9%)	—
15 Gy	20 (30.8%)	—
18 Gy	16 (24.6%)	—

All p = NS. Gy = gray.

systematic approach, 65 patients who did not accomplish these technical requirements for performing an accurate QCA were excluded from the study. Thus, the study population comprised the 65 patients presenting with complete and correct angiographic documentation. All patients, regardless of the dose prescribed (9, 12, 15, or 18 Gy at 1 mm tissue depth), were pooled together.

Of 410 patients enrolled in the balloon arm of the BENESTENT II trial, 179 presenting with all the above-mentioned technical requirements constituted the control group. Baseline characteristics of both the study population and control group are described in Table 1. No differences were observed between the two groups.

Incidence and location of the relocation of the MLD. Relocation pre-post of the MLD was defined in 36 patients (55.4%) in the dose-finding cohort and in 62 patients (34.6%) in the control group (p = 0.005); relocation post-fup was defined in 37 patients (56.9%) in the dose-finding cohort and in 59 patients (33.0%) in the control group (p = 0.001); and relocation pre-fup was defined in 51 patients (78.5%) in the dose-finding cohort and in 47 patients (26.3%) in the control group (p < 0.0001). Geographical miss was identified in two patients (3%). At follow-up, 45 patients (69.2%) presented with an increase in the value of MLD at TS, whereas 20 patients (30.8%) demonstrated either a decrease (18 patients) or no change (2 patients) in the value of MLD at TS. The location of the MLD in cases of relocation is presented in Table 2. This new MLD was most commonly located within the IRS and INS, followed by those regions within the VS but outside the IRS and the INS. Typically, when the new MLD was located outside the INS and IRS, distal subsegments were most often involved rather than the proximal ones (88% vs. 12%, respectively).

Table 2. Location of the Relocated MLD

	Relocation Pre-post (n = 36)	Relocation Post-fup (n = 37)	Relocation Pre-fup (n = 51)
Within INS–IRS	19 (52.9%)	23 (62.2%)	24 (47%)
Outside INS–IRS	9 (25%)	10 (27%)	18 (35.3%)
Within IRS–outside INS	6 (16.6%)	4 (10.8%)	8 (15.7%)
Within INS–outside IRS (geographical miss)	2 (5.5%)	0 (0%)	1 (2%)

INS = injured segment; IRS = irradiated segment.

Methodological implications of the relocation of the MLD. The QCA data derived from the analysis of the predefined regions are shown in Table 3.

DISCUSSION

Incidence and causes of relocation of the MLD. This study demonstrates that the relocation of the MLD is a common phenomenon in coronary segments treated with BA followed by intracoronary beta-radiation therapy. Although relocation of the MLD at follow-up was significantly more frequent in the irradiated group, control patients treated with "plain old balloon" angioplasty also demonstrated a notable incidence of relocation. This phenomenon was noted after radiation was witnessed in previous studies showing that the restenosis process affected the entire vessel segment, which was dilated, and not just the obstructed segment (19,20). To overcome this problem, the Total Occlusion Study of Canada (TOSCA) group devised the concept of "target lesion work length," defined as the length of contiguous target segment exposed to balloon inflation (21). In addition, the relocation of the MLD may explain the mismatch between good angiographic results of

Table 3. QCA Data From the Four Predefined Segments

	TS	INS	IRS	VS
MLD pre (mm)	1.06 ± 0.2	1.06 ± 0.2	1.06 ± 0.2	1.06 ± 0.2
MLD post (mm)	2.17 ± 0.5	1.99 ± 0.4	2.00 ± 0.4	1.91 ± 0.4
MLD fup (mm)	2.36 ± 0.5	1.97 ± 0.5	1.97 ± 0.5	1.84 ± 0.5
%DS fup	20.3 ± 11	33.2 ± 11	33.4 ± 11	37.9 ± 10
Acute gain (mm)	1.12 ± 0.4	0.93 ± 0.4	0.94 ± 0.4	0.85 ± 0.4
Late loss (mm)	−0.18 ± 0.4	0.01 ± 0.4	0.03 ± 0.4	0.07 ± 0.3
Restenosis rate, n (%)	2 (3.1)	5 (7.7)	6 (9.2)	9 (13.8)
Segment length (mm)	5.0 ± 0.3	18.7 ± 4.2	22.9 ± 3.5	36.9 ± 8.4

DS = diameter stenosis; fup = follow-up; INS = injured segment; IRS = irradiated segment; MLD = minimal luminal diameter; pre = pre-intervention; post = post-intervention; TS = target segment; VS = vessel segment.

previous radiation trials and the poor clinical outcome (i.e., high target vessel revascularization rates) observed in these studies (22).

Further, because changes in the reference diameter may occur during the follow-up period, the use of the percent diameter stenosis measurements is questionable as an accurate estimate of lesion severity (19,20). In this regard, two thirds of our study population demonstrated an increase in the value of the preintervention MLD. In the radiation group, increase of vessel dimensions at the site of the index MLD may play an important role in the relocation of the MLD.

Previous three-dimensional IVUS observations demonstrated that the vessel wall enlarges after catheter-based radiation therapy either following conventional BA or stent implantation (12,23). This vessel enlargement was able to accommodate the mean increase in plaque volume, resulting in a net increase in the irradiated luminal volume at follow-up.

In our study, the MLD was mainly relocated within the IRS and the INS and outside the INS and the IRS (typically at distal segments). In such regions, the presence of preexisting plaques that became angiographically apparent or that progressed after the treatment and tapering of the vessel may have accounted for the relocation of the MLD. In addition to these causes of relocation, we cannot exclude the influence of the natural atherosclerotic process on this phenomenon in the context of patients with coronary risk factors by inducing development of new coronary lesions in any of the predefined regions of interest.

Methodological consequences of relocation. When the analysis was restricted to the TS, this lumen gain at follow-up resulted in a negative mean late loss and a very low restenosis rate (3.1%). The TS represents a region that was injured by the balloon and theoretically presented with the peak stress and vessel stretch after BA. Further, this segment was fully covered by the radiation source in all cases. Thus, the results of the analysis of the TS may demonstrate the effect of brachytherapy under optimal conditions. On the other side of the spectrum, when the analysis included the entire VS, both the late loss and the restenosis rate were significantly higher (Table 3). This latter analysis was performed in most of the historical trials aimed to determine effectiveness of new therapeutic agents on the restenosis process after BA (24–27). This traditional approach is driven by the concern that hemodynamic effects (i.e., flow-limiting lesion), symptoms, and outcomes are likely related to the location of the new MLD, irrespective of precise anatomic concordance with its location preintervention. The meticulous analyses proposed are likely to yield new insights on the pathophysiology of this new therapy, and we believe that these are highly recommended during feasibility in vivo and in vitro studies. In clinical radiation trials, the traditional VS approach should be the common angiographic end point, and further analyses of the above-defined regions of interest may complement the results of the study. In this regard, the efficacy of the therapy itself would be determined by the results at the TS, whereas the effectiveness of the radiation therapy would be defined for the entire VS, which includes both the desired (i.e., lumen enlargement) and the side effects (i.e., edge restenosis).

Study limitations. The definition of relocation of the MLD depends decisively on the accurate documentation of all steps followed during the procedure. This was accomplished in only 50% of the cases treated with BA in the dose finding study and in 44% of the historical control group. The QCA data presented in this study represent only the results of the pooled cohort of patients enrolled in the dose finding study, and not the entire population.

Conclusions. Relocation of the MLD is a common phenomenon after successful BA followed by intracoronary beta-radiation. This feature may induce controversial results related to the methodology used in the QCA analysis and should be considered when reporting the results of subsequent radiation studies. The new methodological approach proposed may be useful to determine both the potentialities and the limitations of this new technique.

APPENDIX

The participating centers and investigators of the Dose-Finding Study Group are listed along with the number of included patients in parentheses.

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University Hospital, Kiel, Germany (22): Markus Lins, MD, Simon Ruediger, MD, Gyorgy Kovacs, MD, Thomas Martin, MD, Herrmann Gunhild, MD, Wilhelm Roland, MD, Peter Kohl, MD.

Kings College Hospital, London, United Kingdom (22): Thomas Martin, MD, Francis Calman, MD, Niel Lewis, PhD.

Data monitoring. Thomas Thaler, MD (Boston, Scientific).

Angiographic core-laboratory and data analysis. Yvonne Teunissen, PhD (Clinical Trial Manager), Astrid Spierings, MSc, Connie Van der Wiel, MSc, Gitte Kloek, MSc, Clemens Disco, PhD.

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Chapter 7

Sensitivity and specificity of QCA in detecting coronary arterial remodeling after intracoronary brachytherapy: A comparison to serial volumetric 3-D IVUS analysis Can we detect positive remodeling by luminography?

submitted

Sensitivity and specificity of QCA in detecting coronary arterial remodeling after intracoronary brachytherapy: A comparison to serial volumetric 3-D IVUS analysis Can we detect positive remodeling by luminography?

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Abstract

Background. After the introduction of intracoronary brachytherapy, enlargement of lumen (negative late loss) has been demonstrated. The aim of the study is to analyze the sensitivity and specificity of QCA parameters to detect a positive vessel remodeling as compared to IVUS after intracoronary ß-radiation.

Methods. Twenty-seven patients (27 vessels) treated with balloon angioplasty followed by catheter-based intracoronary ß-radiation with $^{90}Sr/^{90}Y$ source were assessed by both QCA and 3D IVUS with ECG-gated pullback. Irradiated segments were analyzed for total length (30 mm) or each 5-mm subsegment.

Results. Change in MLD was not a predictor for the positive remodeling in both total irradiated segmental and 5-mm subsegmental analysis; 54.3% ROC curve area (95%CI: 30% - 79%, p=NS), 39% sensitivity, 44% specificity, and 55.9% ROC curve area (46% - 66%, p=NS), 55% sensitivity, 54% specificity, respectively. Changes in mean and maximal diameter were not significant parameters to detect positive vessel remodeling as well. When only central subsegments were analyzed, change in MLD was a significant predictor: 63.3% ROC curve area (52-75%), sensitivity 55%, specificity 64% (p=0.029).**Conclusions.** Lumen enlargement detected by QCA does not always mean a positive vessel remodeling after intracoronary radiation. IVUS analysis may be necessary to investigate the mechanism of restenosis after balloon angioplasty followed by catheter-based radiation.

Keywords: intracoronary brachytherapy, quantitative coronary angiography, 3D IVUS, vessel remodeling, balloon angioplasty

INTRODUCTION

For more than a decade, quantitative coronary angiography (QCA) has been the gold standard for the assessment of coronary stenosis because of its accuracy and objectivity as compared to visual and hand-held caliper measurements (1-3). After the introduction of intracoronary brachytherapy, the QCA methodology for the assessment of irradiated coronary had to be adjusted to this new mode of therapy because of the existence of new region of interest; target segment, injured segment, radiated segment and vessel segment(4). In the recent report using catheter-based beta-radiation, enlargement of lumen (negative late loss) has been demonstrated in a subset receiving 18 Gy with balloon angioplasty alone(5). Previously we have reported vessel enlargement accommodating plaque increase in the volumetric 3-D intravascular ultrasound investigation(6). In that report, the lumen remained unchanged at follow-up as an average. In other words, half of the irradiated segments responded to the radiation with a lumen enlargement. Therefore, intracoronary radiation has a potential to increase the lumen diameter(5, 7).
The aim of the study is to analyze the sensitivity and specificity of QCA parameters to detect a positive vessel remodeling as compared to IVUS after intracoronary beta radiation.

METHODS

Patients

The study population consists of 27 patients of 27 vessels. All consecutive patients who underwent balloon angioplasty followed by catheter-based intracoronary ß-radiation with $^{90}Sr/^{90}Y$ source and IVUS imaging with ECG-gated pullback were included. Patients presented with angina pectoris or positive stress testing. Patients with myocardial infarction within 72 hours prior to treatment or left ventricular ejection fraction < 30% were not included in this study. Angiographic inclusion criteria consisted of a reference vessel diameter > 2.5 mm and < 4.0 mm and a lesion length < 20 mm.
The Medical Ethics Committee of the University Hospital Rotterdam Dijkzigt approved the protocol of intracoronary radiation. All patients gave written informed consent.

Radiation System

The source train of the Beta-Cath™ System consists of a series of 12 independent cylindrical seeds, which contain pure ß-emitting $^{90}Sr/^{90}Y$, and is bordered by 2 gold markers (30mm total length of radioactive seeds). The profile of the catheter is 5 French and the source train is not centered. The radiation sources remain at the treatment site for approximately 2-4 minutes to deliver a predetermined dose at 2mm from the centerline of the axis of the source train. Prescribed radiation doses were 12Gy (8 vessels), 14Gy (5 vessels), 16 Gy (9 vessels), and 18Gy (5 vessels).

Procedure

All patients received aspirin (250 mg/day) and heparin IV (10.000 IU) during the procedure and additional heparin was given to maintain the activated clotting time >300sec. Stented patients also received ticlopidine (250mg/day) or clopidgrel (75mg/day) for at least one month. BA was performed according to standard clinical practice. After successful angioplasty, intracoronary β radiation was performed as previously described (8), and repeat angiography and IVUS pullback were carried out. Intracoronary isosorbide dinitrates (200 μg) were administered immediately prior to each of the IVUS pullbacks. At follow-up (6-8 month), further IVUS analysis of the treated vessel was performed.

QCA analysis

QCA analysis was performed off-line by an independent analyst. All angiograms were evaluated after intracoronary administration of nitrates. The analysis was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands). Calibration of the system was based on dimensions of the catheters unfilled with contrast medium. This method of analysis has been previously validated(2, 3). The MLD (minimal lumen diameter) was determined by edge detection and was averaged from the two orthogonal projections. Reference diameter was automatically calculated for the irradiated segment by the interpolated method.

Using the software of the CAAS system, the analyst is able to perform a subsegmental analysis within the region of interest. The segment is automatically divided into subsegments of equidistant length (5.0±0.3 mm).

Additionally, the system computed the mean lumen diameter, maximal lumen diameter and MLD in every subsegment. Late loss was defined as MLD post-treatment minus MLD at follow-up.

IVUS image acquisition and quantitative analysis

The coronary segment subject to 3-dimensional reconstruction was examined with a mechanical IVUS system (CVIS, Boston Scientific Corporation, Maple Grove, MN) incorporating a 30 MHz single-element transducer rotating at 1800 rpm. ECG-gated image acquisition and digitization was performed by a workstation designed for the 3-D reconstruction of echocardiographic images (EchoScan, Tomtec, Munich, Germany). Description of this system has been reported in detail elsewhere(9-11). In brief, the steering logic of the workstation considered the heart rate variability and only acquired images from cycles meeting a predetermined range and coinciding with the peak of the R wave.

A Microsoft Windows™-based contour detection program, developed at the Thoraxcenter, was used for off-line volumetric quantification ADDIN ENRfu (12). Briefly, this program constructed longitudinal sections from the data set and identified the contours

corresponding to the lumen and media boundaries. Volumetric data were calculated by the formula: $V = \sum_{i=1}^{n} A_i * H$, where V = volume, A = area of EEM (external elastic membrane), lumen or plaque in a given cross-sectional ultrasound image, H = thickness of the coronary artery slice, that was reported by this digitized cross-section, and n = the number of digitized cross-sectional images encompassing the volume to be measured. Checking and editing of the contours of the planar images were performed by two independent experienced analysts (KK, ER). Intra-observer variability assessed by analyzing IVUS volumetric studies at least 3 months apart has been reported: -0.4 ± 1.1% in lumen volume, -0.4 ± 0.6% in total vessel (EEM) volume and -0.3 ± 1.0% in vessel wall (plaque + media) volumes using motorized ECG-gated pullback(11). The application of this system has been reported in clinical studies(6, 13-15).

Definitions

Total vessel volume (TVV), lumen volume (LV) and plaque volume (PV) were calculated from the contours of each cross-section by the software as stated above. In order to assess the volumetric changes of the vessel structures after 6-8 months, the delta value for each measurement was calculated (delta (Δ) = follow-up – post-procedure). To eliminate the influence of the vessel size, percent change (delta volume / post-procedure volume) was also calculated.

Remodeling of the vessel wall was defined when total vessel (EEM) volume increased or decreased, compared to post-procedure measurements by at least two standard deviations (± 1.2%) of the intra-observer variability. By using this technique, the potential intrinsic error of the method may be avoided(16-18).

Selection of the region of interest

The segment of interest was selected for QCA after reviewing all cinefilms performed during the index procedure. Any angiographic sequence showing the lesion of pre-intervention, post-intervention, follow-up, and the position of radiation source may be displayed simultaneously on the screen using the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands). The ECG tracing is also displayed in any angiographic sequence. By selecting frames in the same part of the cardiac cycle, we were able to define the location of the radiation source relative to the original lesion (30-mm in length). Sidebranches were used as index anatomical landmarks. Distances from this proximal or distal sidebranches to the inner part of the proximal and distal gold markers were computed by the CAAS software. The segment encompassed by the inner part of the 2 radio-opaque markers defined the irradiated segment (IRS) (Figure 1). All regions of interest were superimposed on the post-procedural and follow-up angiograms.

The methodology to define the segment of interest angiographically using this technique has been described previously(19).

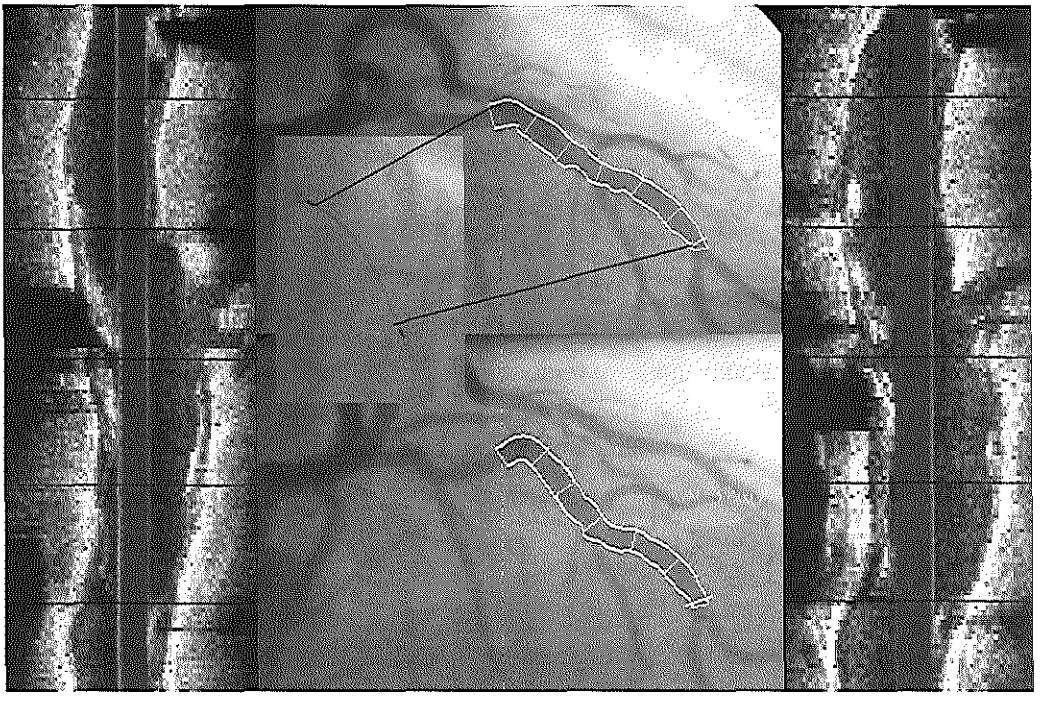

Figure 1
Selection of region of interest
At the time of procedure, radiation source surrounded by contrast was filmed (central upper panel).
From the position of the source related to anatomical landmarks and the distance from them, irradiated segments were selected on IVUS (left side panel).
At follow-up, same segments were identified on angiogram and IVUS by using the anatomical landmarks (central lower panel and right side panel).

By applying the same methodology using the Rubo DICOM Viewer and CAAS system, we were able to define the location of the radiation source train with anatomical landmarks on IVUS (Figure 1). IRS was selected based on the anatomical landmarks and the distances from them calculated by the 3D reconstruction system post-procedure. At follow-up, correct matching of the region of interest was assured by both the use of the same IVUS motorized pull-back system and the comparison of the longitudinal view to that of post-procedure. This methodology for IVUS has been described in detail previously(6, 20, 21).

Statistical analysis

Quantitative data are presented as mean ± standard deviation. The comparisons between the volumetric data were performed using a two-tailed Student's t-test. Categorical data were compared by means of Fisher's exact test. Linear regression analysis was used to investigate the relationship between QCA and IVUS parameters. Sensitivity and specificity were calculated to show the true positive and true negative probability of

positive remodeling (+2.4% increase in TVV). Receiver operator characteristic (ROC) curves were constructed to investigate the diagnostic power of the variable. A value of $p<0.05$ was considered statistically significant.

RESULTS

Irradiated segment analysis (30 mm in length; n=27)

QCA and IVUS data per patient are presented in Table 1. When change in MLD by QCA was used for the detection of positive remodeling, a ROC curve area of 54.3% (95%CI: 29.7% to 78.9%), a sensitivity of 38.9% and a specificity of 44.4% were observed (p=NS). Interpolated reference diameter and maximal diameter of the target vessel did not show significant results as well.

Subsegmental analysis (n=138)

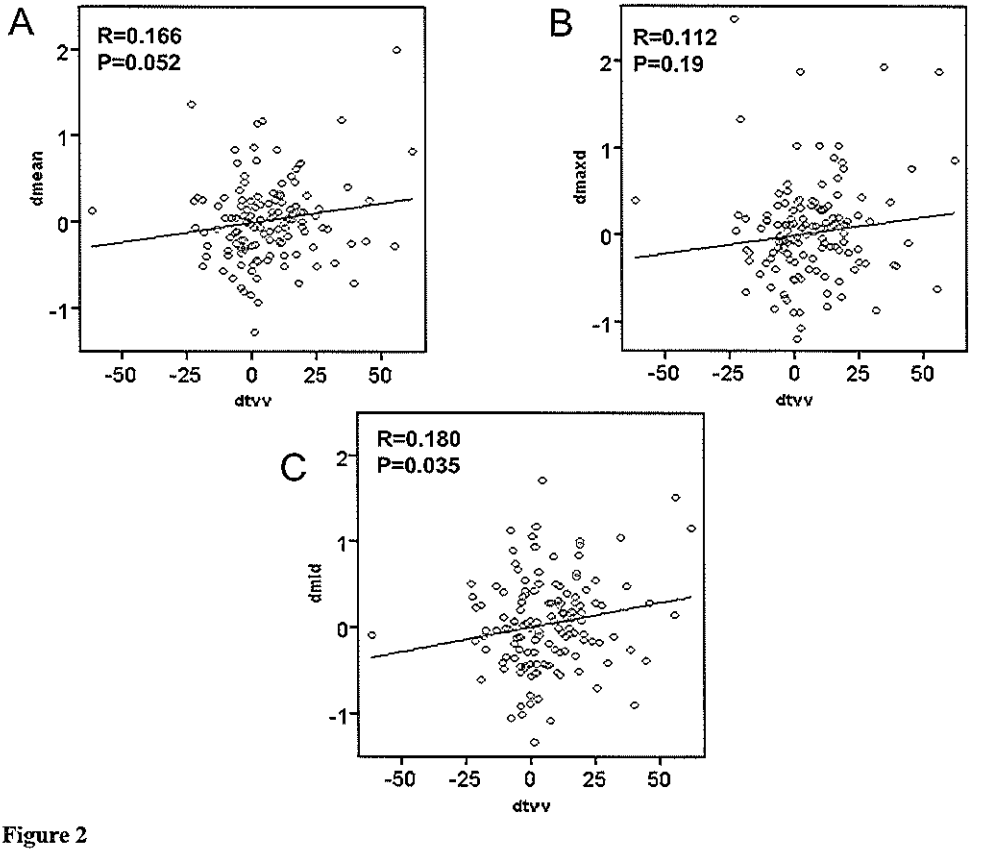

Figure 2

Correlation between QCA parameters and change in TVV (subsegmental analysis)

DTVV = change in total vessel volume, dmean = change in mean diameter of the sub-segment, Dmaxd= change in maximum diameter of the subsegment, dmld = change in minimum lumen diameter of the sub-segment

Table 1. QCA and IVUS data per patient (n=27)

	post	6M	p-value
QCA parameters			
Reference diameter	2.93±0.71	2.95±0.62	0.81
Max lumen diameter	3.75±0.84	3.65±0.60	0.62
Min lumen diameter	2.06±0.68	1.88±0.63	0.08
%diameter stenosis	31.5±7.9	35.0±18.1	0.27
IVUS parameters			
LV	247.5±108.4	249.1±121.5	0.88
TVV	445.3±145.6	481.6±165.0	0.004
PV	197.7±56.6	232.5±66.9	0.001

Table 2. Subsegmental analysis (n=138)

	post	6M	p-value
QCA parameters			
Mean lumen diameter	2.83±0.71	2.81±0.61	0.55
Max lumen diameter	3.23±0.78	3.18±0.65	0.34
Min lumen diameter	2.46±0.69	2.43±0.63	0.40
IVUS parameters			
LV	43.4±22.4	43.2±21.8	0.88
TVV	78.9±28.9	85.1±31.0	0.001
PV	35.5±15.7	41.8±16.3	0.001
Mean lumen diameter	3.25±0.77	3.26±0.71	0.86
Max lumen diameter	3.60±0.83	3.65±0.77	0.34
Min lumen diameter	2.91±0.73	2.89±0.68	0.70
Mean wall thickness	1.19±0.43	1.37±0.41	0.001
Max wall thickness	1.52±0.50	1.70±0.47	0.001
Min wall thickness	0.86±0.37	1.06±0.37	0.001

Table 3. Predictive Values of Positive vessel remodeling (subsegmental analysis)

	ROC area	p-value	95%CI	Sensitivity	Specificity
All subsegments (n=138)					
Delta mean diameter	57.1	0.152	48-67	58%	54%
Delta max diameter	56.3	0.202	47-66	60%	54%
Delta MLD	55.9	0.231	46-66	55%	54%
Central part (n=94)					
Delta mean diameter	62.0	0.048	50-74	55%	64%
Delta max diameter	58.1	0.184	46-70	56%	64%
Delta MLD	63.3	0.029	52-75	55%	64%
Segments where MLD originally located (n=27)					
Delta mean diameter	63.6	0.266	40-87	36%	80%
Delta max diameter	55.7	0.639	47-66	29%	80%
Delta MLD	70.0	0.101	48-92	57%	70%

Subsegmental QCA and IVUS data are shown in Table 2. Twenty-four subsegments were excluded from the final analysis because of diffuse calcified (n=14) or side branches that involved >90° of circumferential arc in >30% of the cross sections (n=10). There were significant increases only in IVUS derived parameters: TVV, PV and any of wall thickness (mean, max and min). Only poor correlation was observed between QCA parameters and change in TVV (Figure2). According to the ROC curve analysis, change in MLD derived from QCA was not a good indicator of positive remodeling with a sensitivity of 55% and a specificity of 54% (Table 3). Changes in mean and maximal diameter were not significant parameters to detect positive vessel remodeling as well.

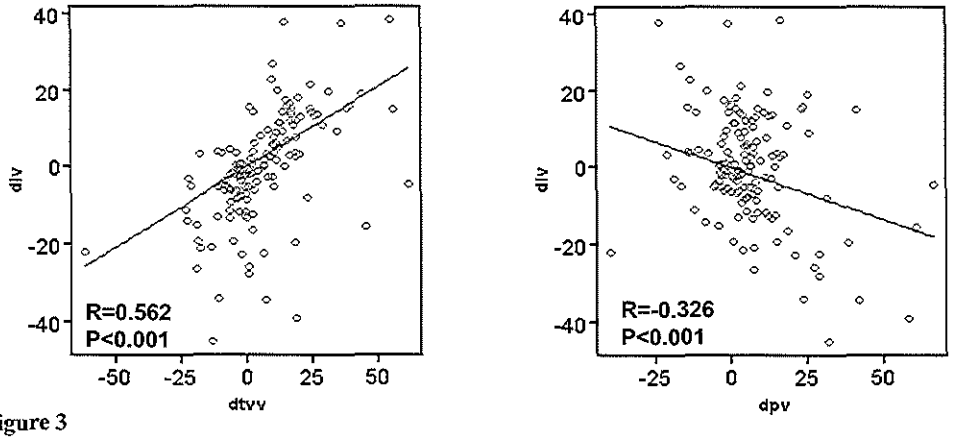

Figure 3
Correlation between change in LV and TVV (left side panel) and LV and PV (right side panel)

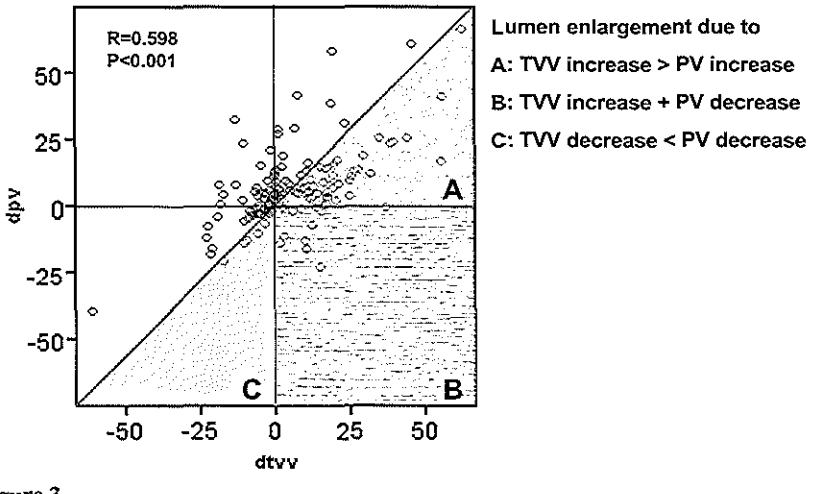

Figure 3
Correlation between change in TVV and PV

Since the radiation source has an acute dose fall off, both extreme subsegments receive lower dose than central part of the irradiated segments(18). When only central subsegments were analyzed, ROC curve area and sensitivity and specificity were better than total subsegments (Table 3).
LV quantified by 3-D IVUS correlates with change in TVV ($r=0.562$, $p<0.001$). Change in mean vessel wall thickness showed a significant but only a weak correlation with change in TVV ($r=0.265$, $p=0.002$). To investigate the lumen determinant, Pearson correlation analysis was performed (Figure3 and 4). Change in lumen volume was partially correlated to the changes in both TVV and PV. Change in TVV is also associated with delta PV. Zone A, B and C in Figure 4 represents lumen enlargement. Majority of subsegments showing lumen increases places in zone A, which demonstrates positive vessel remodeling accommodating tissue growth.

Segments where MLD was initially located (n=27)

It has been reported that relocation of MLD is more frequent in brachytherapy than conventional balloon angioplasty(4). In the current study, relocation of MLD from pre-procedure to post-procedure has occurred in 74% of vessels. Between post-procedure and follow-up, the rate of relocation was 82%. Since MLD is used as a target of the treatment, only segments where MLD was initially located were examined. Changes in mean diameter, maximal diameter and MLD of the segments were not an indicator of positive vessel remodeling as well as the total subsegmental analysis (Table 3).

DISCUSSION

The aim of this study is to investigate the usefulness of QCA in understanding the mechanism of prevention of restenosis by intracoronary brachytherapy. This study demonstrates that parameters derived from QCA are not sufficient to establish the presence of the positive vessel remodeling after balloon angioplasty in the setting of catheter-based β-radiation ($^{90}Sr/^{90}Y$ source). However, mean diameter and MLD were significant indicators for a positive vessel remodeling when fully irradiated segments were considered.
In animal experimental models, it has been emphasized that intracoronary radiation inhibits neointimal proliferation(22-24). However, experimental data have also suggested that radiation have an effect on vessel remodeling by modifying cell responses in the adventitia (25, 26). Whether intracoronary radiation mainly affects positive remodeling or inhibition of tissue proliferation remains to be investigated. It is also a point of debate in human IVUS investigations. Positive vessel remodeling accommodating neointimal ingrowths after 6 months has been demonstrated using 3-D IVUS quantification(6), whereas total vessel area and plaque area remained unchanged in another study(27). In the present study, total vessel volume and wall thickness derived from IVUS was partially correlated to the lumen change (Figure3). Therefore, the contribution of

vessel remodeling and tissue proliferation to the lumen preservation may have different patterns depending on the individual and local elements (local dimensions, delivered dose, plaque morphology and degree of injury). In addition, central part of irradiated segments showed higher sensitivity and specificity with significant ROC curve area in changes in MLD and mean diameter. This finding may demonstrate that higher dose radiation have an effect to reduce the variability of the response, which lead to the vessel enlargement. Dosimetric analysis would be required to address this issue.

QCA has been a standard research tool for more than a decade, providing accurate and reproducible measurements. Most of clinical trials on restenosis after coronary intervention have used angiographic measurements (minimal lumen diameter and % diameter stenosis) for their angiographic end points. However, we recently reported that QCA methodology for the assessment of irradiated coronary arteries had to be adjusted to this new mode of therapy because of the existence of various regions of interest (target segment, injured segment, radiated segment and vessel segment)(4). In addition, lumen enlargement with negative late lumen loss has been rarely reported before the introduction of coronary brachytherapy; Dose-finding study using ^{90}Y source has shown lumen enlargement after catheter-based beta-radiation following balloon angioplasty for the first time(5). There are some important aspects in understanding the mechanism of lumen enlargement detected by QCA. First, radiation can potentially induce positive vessel remodeling (i.e. TVV increase) and medial thinning or thickening (i.e. changes in PV). These various changes in vessel wall and morphology may be one of the reasons for the complexity of vessel response after balloon angioplasty followed by intracoronary radiation (Figure 4). Second point may be the delivered dose of this β-emitting source ($^{90}Sr/^{90}Y$ source). Indeed, dose in homogeneity within the irradiated segments was observed in the previous study(28). In that report, plaque volume at follow-up (comparable to wall thickness at follow-up) was associated with actual dose, which is widely ranged over the entire irradiated segments. In the present study, central fully irradiated segments showed better sensitivity and specificity. These findings suggest that actual delivered dose may be a major determinant of vessel remodeling. It is of note that the actual dose delivered to the adventitia cannot be assessed by QCA. Third, highly frequent relocation of MLD in the present study may also support the variability of the response. This result suggests that the comparison between post-procedure and follow-up is assessed in different positions in most of the cases. Finally, another factor influencing the poor prediction of positive vessel remodeling may be an inaccuracy of edge-detection method of QCA. Especially immediately after the procedure, poor correlation between QCA and IVUS results has been reported because of complex lumen morphology after balloon angioplasty(29). Therefore, lumen increase detected by QCA may not be fully explained by positive vessel remodeling.

Limitations

Small inaccuracies cannot be completely ruled out because of axial movement of the radiation source during the cardiac cycle. However, 3-dimensional reconstructed volumetric IVUS analysis with ECG-gated pullback used in the present study is the most precise method currently available in terms of selection of region of interest by eliminating the artifacts from the cardiac movement. By using this technique, we have demonstrated the behavior of the irradiated vessels comparing the vessel geometry at follow-up with post-procedure(6, 30). To investigate the mechanism of action of radiotherapy, this comprehensive technique representing the entire segment of interest may be more relevant instead of assessing single cross-sectional image or angiographic results, since relocation of MLD frequently occurs after balloon angioplasty followed by intracoronary beta-radiation(4). However, it is nevertheless important to note that the common angiographic end points (i.e. restenosis rate) would be enough to assess the effectiveness of intracoronary brachytherapy in clinical protocols, considering that discrete lesions at follow-up can be well detected by QCA(29).

CONCLUSIONS

Lumen enlargement detected by QCA does not always mean a positive vessel remodeling after intracoronary radiation. IVUS analysis may be necessary to investigate the mechanism of restenosis after balloon angioplasty followed by catheter-based radiation.

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Part II

The Dark Side of Brachytherapy

Chapter 8

Geographic miss: a cause of treatment failure in radio-oncology applied to intracoronary radiation therapy.

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Geographic Miss

A Cause of Treatment Failure in Radio-Oncology Applied to Intracoronary Radiation Therapy

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Background—A recognized limitation of endovascular β-radiation therapy is the development of new stenosis at the edges of the irradiated area. The combination of injury and low-dose radiation may be the precursor of this phenomenon. We translated the radio-oncological concept of "geographic miss" to define cases in which the radiation source did not fully cover the injured area. The aims of the study were to determine the incidence and causes of geographic miss and evaluate the impact of this inadequate treatment on the outcome of patients treated with intracoronary β-radiation.

Methods and Results—We analyzed 50 consecutive patients treated with β-radiation after percutaneous coronary intervention. The prescribed dose ranged between 12 and 20 Gy at 2 mm from the source axis. By means of quantitative coronary angiography, the irradiated segment (IRS) and both edges were studied before and after intervention and at 6-month follow-up. Edges that were injured during the procedure constituted the geographic miss edges. Twenty-two edges were injured during the intervention, mainly because of procedural complications that extended the treatment beyond the margins of the IRS. Late loss was significantly higher in geographic miss edges than in IRSs and uninjured edges (0.84±0.6 versus 0.15±0.4 and 0.09±0.4 mm, respectively; $P<0.0001$). Similarly, restenosis rate was significantly higher in the injured edges (10% within IRS, 40.9% in geographic miss edges, and 1.9% in uninjured edges: $P<0.001$).

Conclusions—These data support the hypothesis that the combination of injury and low-dose β-radiation induces deleterious outcome. (***Circulation.*** **2000;101:2467-2471.**)

Key Words: geographic miss ■ radioisotopes ■ balloon ■ angioplasty ■ stents ■ angiography ■ restenosis

Endovascular radiation therapy is a novel technique aimed at preventing restenosis after percutaneous coronary intervention.[1–3] Radiation can be delivered to the coronary artery by means of catheter-based systems or radioactive stents.[4] A potential drawback of this treatment is the development of new stenotic lesions at both edges of the irradiated segment (IRS). This so-called "edge effect" was originally described after high-activity (>3 μCi) radioactive stent implantation.[5,6] However, this phenomenon is not exclusive to radioactive stents and may also affect coronary segments treated by means of catheter-based systems.[7] The pathophysiology of the edge effect may be the result of vessel wall injury[8–10] concomitant with low-dose radiation at the edges of the irradiated area.[11,12] In radio-oncology, the term to define a cause of treatment failure due to low dose was coined by the Manchester Clinic as "geographic miss." In such cases, a small part of the treatment zone has either escaped radiation or been inadequately irradiated because the total volume of the tumor was not appreciated and hence an insufficient margin was taken.[13] This concept is translated in interventional cardiology to define those coronary segments that were injured but received low-dose radiation. Typically, this phenomenon occurs when the edges of the IRS, where, by definition, the dose is rather low, are injured.

The aims of the study were (1) to determine the incidence and causes of geographic miss in the treatment of patients with intracoronary β-radiation by use of a catheter-based system and (2) to evaluate the impact of this inadequate treatment on the angiographic outcome of these patients.

Methods

Patient Selection

We retrospectively analyzed 50 consecutive patients treated at our institution with catheter-based β-radiation by means of the Beta-Cath system (Novoste Corp). Patients included in the radiation protocol were those with objective signs of ischemia and presence of

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significant de novo lesions (n=39) or recurrent in-stent restenosis (n=11). A detailed description of the radiation system has been reported elsewhere.[14] The radiation source train consists of a series of 12 cylindrical seeds that contain the radioisotope $^{90}Sr/^{90}Y$ sources and is bordered by 2 gold radiopaque markers separated by 30 mm.[14]

Procedure

The medical ethics committee of our institution approved the investigational use of β-radiation, and all patients signed an informed consent form. Percutaneous intervention was performed according to standard clinical practice. Typically, coronary lesions were treated initially with balloon angioplasty (BA). After successful BA, the target coronary segment was irradiated. This could be followed by additional stent implantation when clinically indicated. Lesion length measured on average 11.4±4 mm, the mean balloon length was 20.0±3 mm, and the number of balloon inflations was 2.9±1.6. Patients received aspirin (250 mg) and heparin (10 000 IU IV) at the initiation of the procedure, and an additional dose of heparin was administered to maintain the activated clotting time >300 seconds. After the procedure, aspirin was continued indefinitely. In patients who also received stent implantation, ticlopidine was initiated and continued for ≥15 days after the procedure. The radiation dose was prescribed at 2 mm from the source axis. The prescribed dose for the treatment of de novo lesions was randomly assigned to 12, 14, or 16 Gy for protocol requirements. For the treatment of in-stent restenotic lesions, the prescribed dose was 16 or 20 Gy if the reference diameter, by quantitative coronary angiography (QCA), measured ≤3.25 mm or >3.25 mm, respectively. The mean dwell time to deliver these doses was 143±44 seconds.

Definitions

The IRS was defined as the area encompassed by the 2 gold markers of the radiation source train. It was identified on angiography by a contrast injection with the source in place. The edges of the IRS were defined as the 5-mm-long segments proximal and distal to the angiographic location of the gold markers. The edges that were touched by the angioplasty balloon or received new stent implantation during the procedure were defined as geographic miss edges, because they represent injured segments receiving low-dose radiation. Uninjured edges were those that were not traumatized during the intervention. To determine whether the edges of the IRS were injured, a few steps were followed: during the procedure, every balloon inflation or additional stent implantation was filmed in the same projection, as was the radiation source. This approach allowed us the correct matching of the cine films in the offline analysis. Either cine loop showing balloon inflation, stent implantation, and radiation source may be displayed simultaneously on the screen with the Rubo DICOM Viewer (Rubo Medical Imaging). ECG tracing is also displayed in either cine loop. By selecting those frames in the same part of the cardiac cycle, we were able to define the location of the radiation source relative to the injured area.

QCA Analysis

The IRS and both edges were analyzed by QCA before and after intervention and at 6-month follow-up. All angiograms were evaluated after intracoronary administration of nitrates. The offline analysis of 2 orthogonal projections was performed by means of the CAAS II analysis system (Pie Medical BV). Calibration of the system was based on dimensions of the catheters not filled with contrast medium. This method of analysis has been previously validated.[15–17] The following QCA parameters were computed in the IRS and both edges: minimal luminal diameter (MLD), which was computer defined; reference diameter, which was obtained by an interpolated method[15–17]; and percentage diameter stenosis. Binary restenosis was defined in every area as diameter stenosis >50% at follow-up. Acute gain was defined as MLD after treatment minus MLD before intervention. Late loss was defined as MLD after treatment minus MLD at follow-up. Relative late loss was defined as late loss divided by reference diameter.[18]

Statistical Analysis

To compare continuous variables between IRS, geographic miss edges, and uninjured edges, 1-way ANOVA with post hoc analysis for multiple comparisons was performed. Unpaired Student's t test was performed to compare continuous variables between proximal and distal geographic miss edges and between patients in whom the geographic miss was induced by balloon dilatation or stent implantation. To compare the binary restenosis between groups, the χ^2 test was performed. All tests were 2-tailed, and a value of $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

Fifty irradiated coronary arteries and 100 edges in 50 patients were eligible for the study. However, 26 edges were excluded because of the ostial location of the proximal end of the source in the right coronary artery (n=12) or overlapping of 1 of the edges with side branches (n=14). Thus, finally, 74 edge areas and 50 IRSs were studied. Mean age was 55.3±9 years, and 38 patients (76%) were male. Smoking was the most frequent coronary risk factor, involving 33 patients (66%), followed by dyslipidemia in 27 patients (54%) and hypertension in 24 patients (48%). Eight patients (16%) were diabetic. The left anterior descending coronary artery was treated in 21 patients, the left circumflex in 10, the right coronary artery in 18, and a saphenous vein graft in 1. Twelve patients received a stent in a bailout situation.

Incidence and Causes of Geographic Miss

Geographic miss was observed in 22 edges (31.9%) induced by balloon dilatation (n=13) or additional stent implantation (n=9). The remaining 51 edges (68.9%) were defined as uninjured edges. The location of the geographic miss was in the proximal edge in 11 patients (50%) and in the distal margin in 11 patients (50%). The following reasons were responsible for this phenomenon: (1) development of procedural complications that extended the treatment beyond the margins of the IRS (unexpected geographic miss, n=9); (2) lack of availability of a longer radiation source (>30 mm) in patients with diffuse recurrent in-stent restenosis in whom radiation was given on a compassionate-use basis (n=8); and (3) lack of accurate matching: ie, the injured segment from previous balloon inflations was not appropriately covered by the source (n=5). An example of a patient with geographic miss induced by a balloon dilatation in the proximal margin is depicted in Figure 1.

QCA Analysis

QCA data are presented in the Table. As expected, IRSs demonstrated, on average, a higher acute gain than both injured and uninjured edges. However, geographic miss edges presented, on average, with significantly higher late loss and relative late loss. Restenosis was demonstrated in 5 cases (10%) within the IRS, in 9 cases (40.9%) in the geographic miss edges, and in 1 case (1.9%) in the uninjured edges ($P<0.001$). No difference in the pattern of the late loss between the 3 areas was observed in de novo lesions compared with recurrent in-stent restenotic lesions (Figure 2). In the geographic miss edges, 4 edge restenoses (44%) were located at the proximal edges, whereas the other 5 (56%)

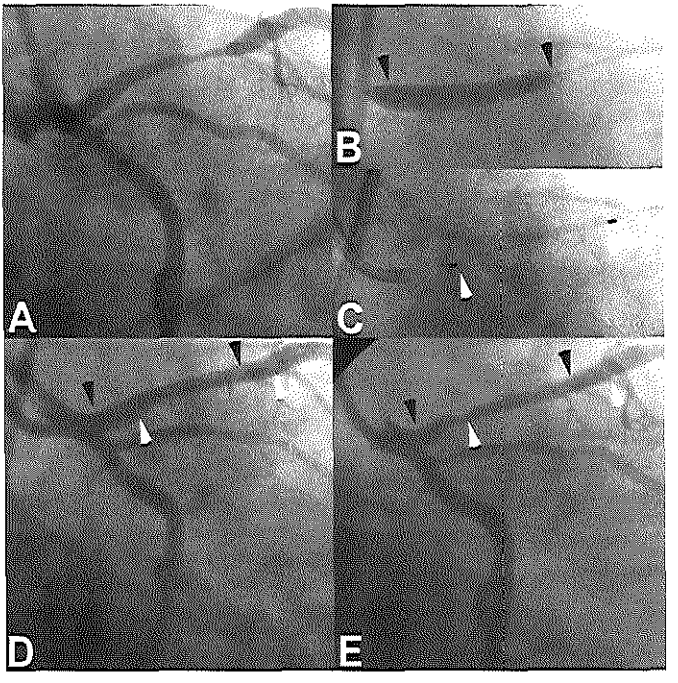

Figure 1. Geographic miss induced by balloon dilatation. A, Lesion located in proximal segment of left anterior descending coronary artery. B, Balloon dilatation performed during intervention (black arrowheads indicate area injured by balloon). C, Radiation source train in place. Irradiated area is delimited by gold markers (white arrowheads). D, Final result: proximal traumatized edge presented a residual type B dissection. E, At 6-month follow-up: obvious reduction in lumen at geographic miss edge.

were located at the distal edges. Mean relative late loss was comparable between those edges, with geographic miss located proximal or distal to the IRS (0.31±0.2 versus 0.34±0.2, respectively; P=NS). Those edges in which the geographic miss was due to additional stent implantation presented, on average, higher acute gain than those due to balloon dilatation (0.70±0.4 versus 0.21±0.3, respectively; P=0.005). However, mean late loss and mean relative late loss were comparable between both causes of geographic miss (0.95±0.9 mm and 0.36±0.3, respectively, after stent versus 0.77±0.3 mm and 0.30±0.1 after balloon dilatation; both P=NS).

Discussion

This study reports on the initial experience of our center with the use of intracoronary β-radiation. By means of a careful retrospective angiographic analysis of all patients treated with the same radiation system, we sought to define the effect of the injury on those areas located at the margins of the source where the delivered dose is potentially rather low. Up to 31.9% of the patients presented with the predefined technical error, called geographic miss. This concept requires the concurrence of 2 conditions: low-dose radiation and injury. Any other clinical situations that do not include both conditions cannot be called geographic miss. For instance, (1) the effect of injury on coronary segments not being irradiated (proximal or distal to an IRS but in areas in which the calculated dose is almost 0) should fall into the category of normal restenotic process; (2) the effect of low-dose radiation in areas that have not been injured may be defined as the pure radiation edge effect, because in intracoronary radiation, the

QCA Data

	IRS (n=50)	Geographic Miss Edges (n=22)	Uninjured Edges (n=52)	*P*
MLD before intervention, mm	1.20±0.3	2.02±0.6	2.10±0.6	<0.0001
MLD after intervention, mm	2.02±0.4	2.43±0.5	2.12±0.6	0.01
MLD at follow-up, mm	1.87±0.5	1.59±0.6	2.02±0.5	0.006
Reference diameter, mm	2.69±0.6	2.50±0.6	2.55±0.7	NS
%DS before intervention, %	54.9±13	19.8±14	17.9±11	<0.0001
%DS after intervention, %	28.4±9	19.9±10	20.8±11	0.0003
%DS at follow-up, %	33.3±11	44.3±22	24.3±10	<0.0001
Acute gain, mm	0.81±0.4	0.41±0.4	0.01±0.3	<0.0001
Late loss, mm	0.15±0.4	0.84±0.6	0.09±0.4	<0.0001
Relative late loss	0.06±0.1	0.32±0.2	0.02±0.1	<0.0001

%DS indicates diameter stenosis. Data are mean±SD.

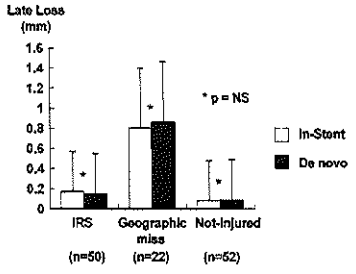

Figure 2. Difference in late loss between IRS, geographic miss edges, and uninjured edges. De novo lesions and in-stent restenosis demonstrated same degree of late loss between 3 groups.

edges of any IRS will always receive low-dose radiation; and (3) finally, the effect of a full prescribed dose on segments presenting with or without injury is the situation in which the physician may be able to irradiate (with full dose) the entire injured segment and include some uninjured margin. A key issue in the definition of geographic miss is to define those segments receiving a low dose. These may vary between systems and sources used. With the Beta-Cath system, the longitudinal distance of the 100% isodose is 26 mm. Because the β-emitting $^{90}Sr/^{90}Y$ has an acute falloff of dose related to the distance,[19] the last 2 mm within the markers of the source should be considered as having received a lower than prescribed dose. In fact, the dose received at 1 mm from the 100% isodose is 86% of the prescribed dose, and at 2 mm, 60% of the prescribed dose (inner part of the gold marker). At 3 mm, the dose is 30% of the prescribed dose; at 4 mm, 13% of the prescribed dose; and at 5 mm, 5% of the prescribed dose. We defined the IRS as the segment encompassed by the 2 gold markers, which included the last 2 mm within the markers with a lower than prescribed dose (up to 60% of the prescribed dose). By this definition, late loss and restenosis rate were significantly lower than those of the injured edges (analyzed from the inner part of the gold marker). Furthermore, the 5 cases of restenosis within the IRS were located at the site of the initial MLD. These results may reflect the fact that the dose at these last seeds of the source was high enough to avoid the edge effect after the edges had probably been injured during the procedure, especially when a 20-mm-long balloon was used. Thus, the region receiving a low dose may be defined, for this system and source, as the 5-mm-long segment located 2 mm farther from the 100% isodose boundary, that is, beyond the inner part of the gold marker. In this regard, we believe that the injury should be completely restricted to the segment of the 100% isodose curve of the radiation source (26 mm) and that the last 2 mm at both extremities of the source and within the gold markers may be considered relatively but probably not completely safe. Finally, any injured segment covered by or beyond the gold marker (up to 5 mm) must be considered to be at high risk of failure at follow-up.

From the perspective of these findings and future technical developments in the field, the following recommendations are advisable. Filming every single balloon inflation performed during the procedure would allow one to define the injured area. More than ever, tenacious attention to detail in positioning the radiation catheter encompassing the entire injured area must be mandatory. The development of longer sources (>30 mm) would allow one to treat diffuse lesions and completely cover those areas in which an extension of the treatment was indicated because of procedural complications. Equally, the use of online QCA in the decision-making would avoid appreciation errors due to visual assessment of the target area and subsequent underestimation or overestimation of balloon lengths. Finally, the selection of the most suitable fluoroscopic projections (eg, less foreshortening, no overlapping) would avoid errors in the quantification of the region of interest.

The facts that the locations of most of the restenoses were in geographic miss edges and that late loss in those areas was unexpectedly high must raise an alarm about the deleterious effect of the combination of injury and low-dose radiation. This hypothesis may be supported by the fact that the late loss observed in those injured edges is higher than that reported in recent clinical trials after either BA or stent implantation[20,21] and higher than that demonstrated in the uninjured edges. Balloon overstretch injury has been used as an experimental model to study the restenosis process.[8–10] The response of the vessel wall to injury involves both neointimal hyperplasia[8,9] and vessel remodeling.[10,22,23] The stimulatory effect of low-dose radiation after BA on smooth muscle cell proliferation has been reported previously.[11] In the low-dose radiation group of this swine model (10 Gy), neointima was composed of smooth muscle cells, with a marked increase in inflammatory cells and less medial and intimal fibrosis than in the higher-dose groups (15 and 20 Gy) and the control group. It was suggested that at low dose, inadequate fibrosis was induced to prevent effective smooth muscle cell migration and to act as a diffuse barrier for mediators of chemotaxis, chemokinesis, and cellular proliferation.[11] Similarly, after low-activity radioactive stent implantation (1 μCi) in a porcine model, neointimal hyperplasia was significantly greater than that after nonradioactive control stents.[12] If ongoing intravascular studies reveal that edge restenosis is mainly due to plaque increase, the former hypothesis that at a low dose, inadequate medial and intimal fibrosis to avoid migration and proliferation predominates may become a plausible explanation. Conversely, if negative remodeling is the main contributor to the lumen loss, the excess of inflammatory cells demonstrated at low dose may be responsible for subsequent adventitial fibrosis and vessel shrinkage. The development of the so-called "candy wrapper" after radioactive stent implantation[5] may represent the clinical paradigm of the combined deleterious effect of low-dose radiation and injury. The latter is secondary to the angioplasty balloon used for predilatation and postdilatation of the radioactive stent. In this regard, a higher balloon-to-artery ratio was associated with the presence of this phenomenon.[5]

Future trials must address the benefit of new technical developments in the field (use of square deployment balloons; hot-end, cold-end stents[6]; longer sources with smaller radiation delivery catheters) to minimize the impact of injury at the edges after either radioactive stent– or catheter-based systems.

Study Limitations

In this study, only 1 type of radiation delivery catheter using the β-source $^{90}Sr/^{90}Y$ was evaluated. Thus, the effect of either other catheter-based systems using centering balloons and different sources or the γ-radiotherapy on the geographic miss edges cannot be extrapolated from our results.

The actual dose at the margins of the radiation source has not been calculated. A low dose at these edges was assumed because the isotope $^{90}Sr/^{90}Y$ demonstrates an acute falloff related to the distance from the 100% isodose boundary.[19]

This angiographic study was aimed at defining the concept and the clinical implications of the geographic miss. To define the mechanism of the unexpectedly high late loss and the correlation between radiation dose and plaque extent at the margins of the IRS, intravascular ultrasound studies must be carried out.

The location of the segment receiving a low dose may vary between systems and sources. Thus, the confidence margin to be taken may vary accordingly.

The position of the source relative to the various balloon inflations was assessed by comparing still frames at the same part of the cardiac cycle from cineangiograms performed in the same projections. However, small inaccuracies in the definition of the IRS and the edges, derived from the axial movement of the radiation source during the cardiac cycle, cannot be completely ruled out.

This study was not placebo-controlled. Thus, the effect of the sham source on the balloon-injured coronary segments has not been determined.

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Chapter 9

Two-year follow-up of catheter based ß-radiation. Late events of BERT trial and PREVENT trial

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Two-Year Follow-up of Catheter-Based Intracoronary ß- Radiation Following Percutaneous Intervention: Late Events of BERT and PREVENT trial

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ABSTRACT

Background: Limited data are available on intracoronary brachytherapy for de novo applications and the long-term (2-year) outcome after β-radiation is still unknown.

Methods and results: The population consists of 50 consecutive patients. Intracoronary β-radiation was performed using a ^{90}Sr/Y (Novoste Beta-Cath™) System (n=30) or 32P (Guidant) System (n=20). Clinical data were obtained by clinic visit or telephone contact as required per protocol (mean 26.0 3.5 months). No deaths were observed in this population. In hospital and 30 days events were rare (1 patient of non-Q MI). During the first 6 months, TVR rate was 22%. The incidence of MI still increased after 6 months. Two years after the index procedure, 6 patients (5 non-Q MI and 1 Q MI) had suffered this event. Between 6 months and 1 year, one patient underwent TVR subsequent to MI. Three patients (6%) underwent TVR between 1 and 2 years. Event free rates from death or MI were 96.0% at 6 month, 89.8% at 1 year, and 87.7% at 2 year. MACE free survival rates were 89.9% at 6-month, 71.2% at 1 year, 69.1% at 2 year.

Conclusion: Conventional 6-month follow-up may not be long enough for clinical radiation studies, considering that late occurrence of clinical event is not negligible.

Key words: Brachytherapy, angioplasty, stent, long-term, late thrombosis

Background

Feasibility and short-term safety of catheter-based intracoronary γ or β-irradiation has been demonstrated in clinical trials[1-4]. Randomized studies using intracoronary γ-radiation have reported a significant reduction of restenosis and neointimal proliferation in patients with in-stent restenosis[4,5]. Recently, β-irradiation has also shown to reduce the recurrence rate of restenosis[6,7]. Although the overall clinical benefit of radiotherapy

over placebo in SCRIPPS trial was sustained after 3 years, it is important to note that a considerable angiographic late lumen loss was observed in the irradiated vessels[8]. The outcome after catheter-based β-irradiation over 1-year is still unknown. Incidental reports of late side-effects of radiation therapy such as late onset of thrombotic occlusion[9] or progression of tissue growth[10 11] have raised concern.

The aim of the present report is to document the long-term (2-year) clinical outcomes of patients treated with intracoronary catheter-based β-radiation therapy in a single center.

METHODS

Patients

From April/97 to Sep/98, 50 patients (50 lesions) were consecutively treated with catheter-based intracoronary ß-radiation using the Beta-Cath System™ (Novoste Corp., Norcross, GA) with $^{90}Sr/^{90}Y$ source or the Guidant intracoronary radiation system (Guidant Corp., Houston, TX) with ^{32}P source. Thirty patients were enrolled in the BERT trial and 20 were included in the PREVENT trial. Inclusion and exclusion criteria have been reported[1,7]. Baseline demographic data are summarized in Table 1. The Medical Ethics Committee of the University Hospital Rotterdam approved the protocols and all patients gave written informed consent.

Radiation systems and procedure

The source train of the Beta-Cath™ System consists of a series of 12 independent cylindrical seeds, which contain pure ß-emitting $^{90}Sr/^{90}Y$, and is bordered by 2 gold markers (30mm total length of radioactive seeds). The profile of the catheter is 5 French and the source train is not centered. The radiation sources remain at the treatment site for approximately 2-4 minutes to deliver a predetermined dose at 2mm from the centerline of the axis of the source train. Prescribed radiation doses were randomized to 12Gy (10 vessels), 14Gy (10 vessels), 16 Gy (10 vessels). The Guidant radiation system includes a 0.018-inch nitinol wire with 27 mm of ^{32}P source at its tip. The centering catheter is a double-lumen catheter with a short monorail tip and a spiral balloon, with diameters of 2.5, 3.0 and 3.5 mm, which centers the source within the lumen. The duration of the treatment is calculated based on prescribed dose, which is also calculated from the mean reference vessel diameter by IVUS measurement. Prescribed radiation doses were randomized to 28Gy (6 vessels), 35Gy (9 vessels), 42Gy (5 vessels) at 0.5-mm depth into the vessel wall.

All patients received aspirin (250 mg/day) and heparin IV (10.000 IU) during the procedure and additional heparin was given to maintain the activated clotting time >300sec. Stented patients also received ticlopidine (250mg BID) for 1 month. After successful angioplasty, intracoronary β radiation was performed as previously described [1,7].

Table 1. Baseline Characteristics

	BERT (n=30)	PREVENT (n=20)
Age	57±9	55±9
Male	21 (70%)	15 (75%)
Unstable angina	10 (33%)	7 (35%)
Coronary risk		
Hypercholesterolemia	12 (40%)	12 (60%)
Diabetes	6 (20%)	1 (5%)
Hypertension	8 (27%)	5 (25%)
Smoking	14 (47%)	12 (60%)
Family history	15 (50%)	4 (20%)
Lesion		
Restenotic lesion	0	4
LAD	15	6
LCX	7	4
RCA	8	6
Use of stent	8	8
Lesion length (mm)	13 ± 4	11 ± 2

Follow-up

Clinical data were obtained by clinic visit or telephone contact as required per protocol (2 weeks, 1, 3, 6, 9, and 12 months) and at 24-month (mean 26.0 ± 3.5 months, range 22 to 30 months). All patients were requested to return for repeat coronary angiography at 6 months. Repeat revascularization was performed only if the patient had recurrent symptoms or if exercise tests demonstrated the presence of ischemia.

Myocardial infarction (MI) was defined as the presence of new Q waves (Q MI) or elevation of CPK to greater than two times the baseline with the MB fraction greater than twice the normal value defined by the clinical laboratory (non-Q MI). Target lesion revascularization (TLR) was defined as repeat revascularization (coronary angioplasty or bypass surgery) for restenosis involving the target site. Target vessel revascularization (TVR) was defined as revascularization (angioplasty or bypass surgery) of the target vessel because of the presence of significant stenosis. Major adverse clinical events (MACE) were defined as the composite of death, MI (Q and non-Q wave), and TVR.

Table 2. Cumulative clinical events

	30 days	6-month	1-year	> 1-year
Ranking				
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Death or MI	1 (2%)	2 (4%)	5 (10%)	6 (12%)
Death, MI, or TLR	2 (4%)	11 (22%)	12 (24%)	13 (26%)
Death, MI, or TVR	2 (4%)	12 (24%)	14 (28%)	16 (32%)
No MACE	48 (96%)	38 (76%)	36 (72%)	34 (68%)
Total count of events				
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MI	1 (2%)	2 (4%)	5 (10%)	6 (12%)
TLR	1 (2%)	10 (20%)	11 (22%)	13 (26%)
TVR	1 (2%)	11 (22%)	12 (24%)	15 (30%)
Non-TVR	0 (0%)	2 (4%)	3 (6%)	3 (6%)
Thrombotic event (VF)	0 (0%)	1 (2%)	1 (2%)	1 (2%)

Statistics

Kaplan-Meier analysis was performed for the long-term survival rates. Differences between balloon treated and stented groups and between ^{90}Sr and ^{32}P sources were compared with the use of Log-rank test.

RESULTS

Cumulative clinical events with ranking and total event counts are listed in Table 2. No deaths were observed in this population. In hospital and 30 days events were rare (1 patient of non-Q MI). Besides myocardial infarction, one patient was readmitted to the hospital 2 months after the procedure because of ventricular fibrillation. Angiogram at 6 months revealed total occlusion of the treated segment. During the first 6 months, the incidence of restenosis followed by TVR was 22%. The incidence of MI still increased after 6 months. Two years after the index procedure, 6 patients (5 non-Q MI and 1 Q MI) had suffered this event, mainly due to late thrombotic occlusion (n=5, 10%) of the irradiated target vessel (Figure 1). Two patients (12.5% of stent population) out of 5 who experienced late thrombosis had received a stent, and the other 3 had received balloon

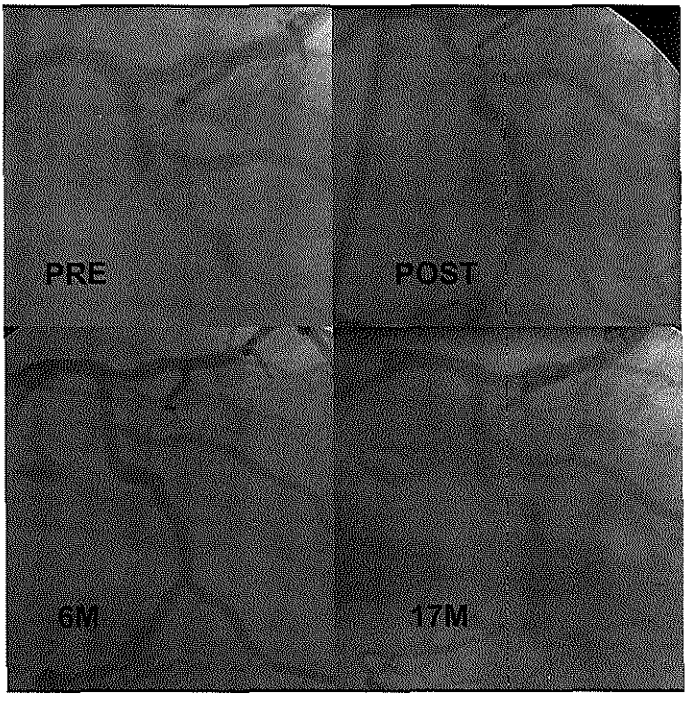

Figure 1
A case of late thrombotic occlusion occurred at 17 months after irradiation

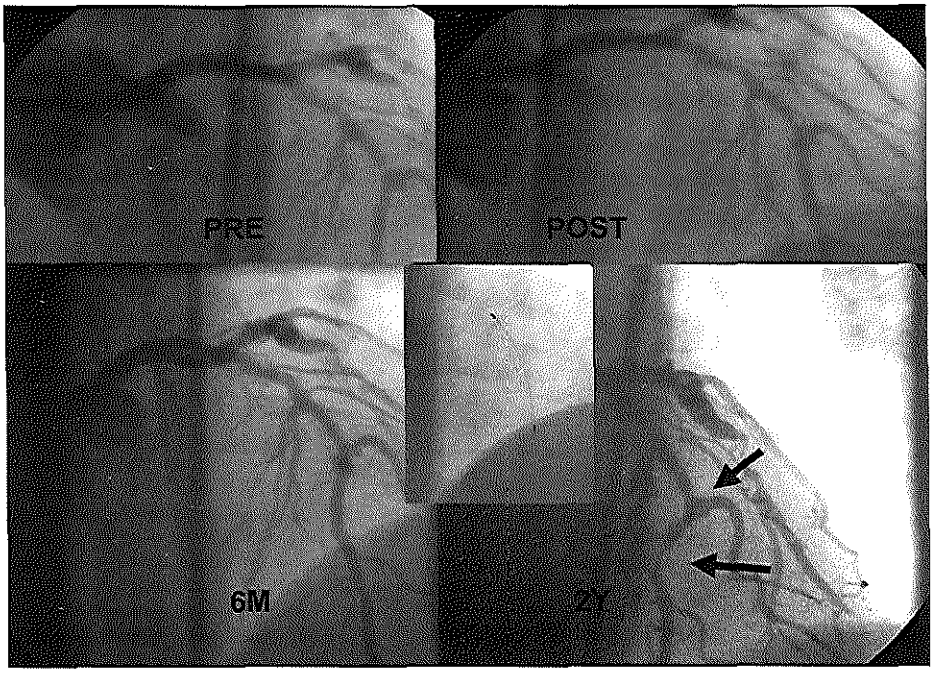

Figure 2
A case of late target vessel revascularization 2 years after irradiation

angioplasty (8.8% of balloon population). Between 6 months and 1 year, the rate of TVR did hardly change (one patient underwent TVR subsequent to MI), but 3 patients (6%) underwent redilatation of the irradiated segments between 1 and 2 years. Of these, one patient suffered an inferior non-Q wave MI at 9 months. One underwent re-dilatation of the index lesion at 1.4 years after radiation and the other received TVR at 2.7 years for a distal lesion but located in the irradiated segment (Figure 2).

According to the Kaplan-Meier analysis, freedom from death or MI were 96.0% at 6 month, 89.8% at 1 year, and 87.7% at 2 year (Figure 3). MACE free survival rates were 89.9% at 6-month, 71.2% at 1 year, 69.1% at 2 year (Figure 4). Survival curves for groups treated with stents or balloon angioplasty are also included in Figure 3 and Figure 4. The outcomes of patients treated with ^{90}Sr and ^{32}P sources were similar (p=NS).

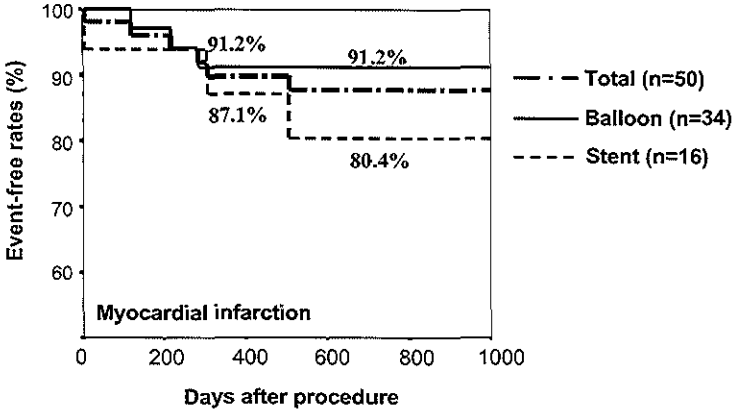

Figure 3
Event free rates from myocardial infarction in total population, balloon treated patients, and stent implanted patients. There was no significant difference between balloon angioplasty and stenting (p=0.19).

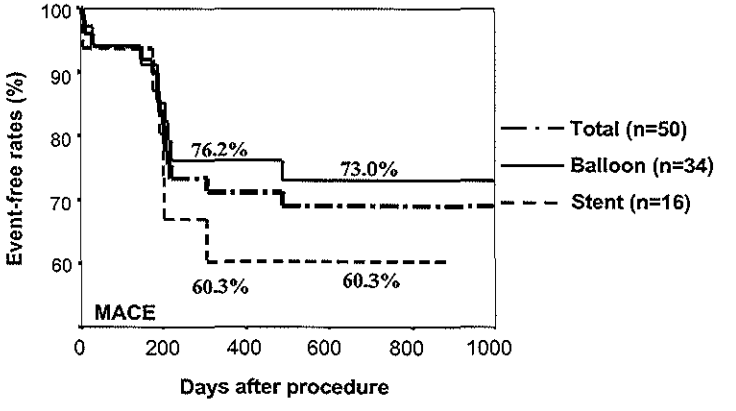

Figure 4
Event free curves from composite MACE in total population, balloon treated patients, and stent implanted patients. There was no significant difference between balloon angioplasty and stenting (p=0.30).

DISCUSSION

The objective of this study was the assessment of long-term (2-year) events after intracoronary β-radiation therapy. The main finding in the current study was a considerable event rate after 6 months mainly due to late MI.

MI considerably increased after 6 months in the study. All of these cases were associated with late thrombotic occlusion of the irradiated vessels. It has been shown that the rate of MI after 6 months in both conventional balloon angioplasty and stenting were rather rare (0.3% and 0.8% increases between 7 months and 1 year in BENESTENT trial, respectively)[12]. Our results confirmed previous reports showing increased thrombogenicity induced by the radiation[9,13,14]. Retrospectively, the duration of ticlopidine regimen of 1-month was not long enough in our series. Prolonged anti-platelet therapy up to 2 years may improve the outcome of patients treated with catheter-based radiotherapy[15]. However, only few data are available from brachytherapy trials employing this longer antiplatelet therapy, extending beyond 1-year.

MACE free rate of 69.1% at 2-year in the current study may be comparable to that of radiation group (61.5%) in the previous report using γ-radiation for in-stent restenosis[16]. Considering that treatment of in-stent restenosis without radiation has a higher MACE rate, the merits of the radiation therapy in the present study population may be less than the population with in-stent restenosis. In fact, when only stented patients are taken into account, the outcomes after brachytherapy (MACE free rates of 60.3% at 1- and 2-year) seem worse than conventional stenting in BENESTENT trial (76.6% at 1-year, 75.8% at 2-year)[12]. Conversely the outcomes (MACE free rates of 76.2% at 1-year and 73.0% at 2-year) of balloon treated patients after brachytherapy seems better than conventional treatment with balloon angioplasty only (68.4% at 1-year, 67.6% at 2-year)[12]. It has been shown that intracoronary radiation inhibits neointimal hyperplasia and constrictive remodeling in most of experimental models and clinical studies[17,18]. Since stents eliminate not only the remodeling component of the restenotic process but also the adaptive enlargement observed with radiation after balloon angioplasty, their role in the setting of catheter-based radiation therapy may be questionable[19]. It is of note that systematic angiographic follow-up in these pilot studies may increase the TVR and total event rates[20]. Whether these relatively high events are related to the radiation treatment itself remains to be investigated in large randomized trials.

One important concern in the field of intracoronary radiation is the potential for late proliferative response. In the current study, only 2 patients received repeat coronary intervention because of restenosis later than 1 year although their initial follow-up of angiograms at 6 months did not show restenosis. It is nevertheless important to note that both experimental and clinical studies have demonstrated delayed lumen deterioration after both catheter-based radiation and radioactive stenting[8,10,11].

Conclusions

Conventional 6-month follow-up may not be long enough for clinical radiation studies, considering that late occurrence of clinical event is not negligible.

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Chapter 10

Radioactive stents delay but do not prevent in-stent neointimal hyperplasia.

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Radioactive Stents Delay but Do Not Prevent In-Stent Neointimal Hyperplasia

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Background—Restenosis after conventional stenting is almost exclusively caused by neointimal hyperplasia. β-Particle–emitting radioactive stents decrease in-stent neointimal hyperplasia at 6-month follow-up. The purpose of this study was to evaluate the 1-year outcome of ^{32}P radioactive stents with an initial activity of 6 to 12 μCi using serial quantitative coronary angiography and volumetric ECG-gated 3D intravascular ultrasound (IVUS).

Methods and Results—Of 40 patients undergoing initial stent implantation, 26 were event-free after the 6-month follow-up period and 22 underwent repeat catheterization and IVUS at 1 year; they comprised half of the study population. Significant luminal deterioration was observed within the stents between 6 months and 1 year, as evidenced by a decrease in the angiographic minimum lumen diameter (−0.43±0.56 mm; P=0.028) and in the mean lumen diameter in the stent (−0.55±0.63 mm; P=0.001); a significant increase in in-stent neointimal hyperplasia by IVUS (18.16±12.59 mm^3 at 6 months to 27.75±11.99 mm^3 at 1 year; P=0.001) was also observed. Target vessel revascularization was performed in 5 patients (23%). No patient experienced late occlusion, myocardial infarction, or death. By 1 year, 21 of the initial 40 patients (65%) remained event-free.

Conclusions—Neointimal proliferation is delayed rather than prevented by radioactive stent implantation. Clinical outcome 1 year after the implantation of stents with an initial activity of 6 to 12 μCi is not favorable when compared with conventional stenting. ***(Circulation.* 2001;103:14-17.)**

Key Words: radioisotopes ■ restenosis ■ stents ■ angiography

Implantation of ^{32}P radioactive stents with activities ranging from 3.0 to 12 μCi in coronary artery lesions has been reported to inhibit neointimal hyperplasia within the stent at 6-month follow-up.[1,2] The major limitation of this therapy is significant renarrowing at the stent edges, which is called the "candy wrapper" or "edge effect."[1] Catheter-based radiation significantly reduces the recurrence of restenosis 6 months after percutaneous transluminal coronary angioplasty for in-stent restenosis, but 3-year follow-up reveals greater luminal deterioration in γ-radiation–treated patients.[3,4] Such findings indicate the need for longer follow-up beyond the traditional 6 months in patients treated with intracoronary radiation. The purpose of this study was to assess late results after the implantation of radioactive stents using repeat catheterization with quantitative coronary angiography and 3D intravascular ultrasound (IVUS) at 1 year.

Methods

Patient Population

The European ^{32}P Dose-Response Trial was a nonrandomized multicenter trial evaluating the safety and efficacy of implanting radioactive stents with activity levels of 3 to 12 μCi in single, native coronary artery lesions. All stents were implanted in de novo lesions, except for 1 case of in-stent restenosis. For the purposes of this analysis, this case was excluded. Other inclusion and exclusion criteria, as well as immediate and 6-month results, were previously reported.[1,2] Only patients undergoing 6-month angiographic and IVUS follow-up who did not experience major adverse cardiac events during the first 6 months were included. The study was performed in accordance with the Declaration of Helsinki and the European Guidelines for Good Clinical Practice. Ethical approval was provided by the Medical Ethical Committee of the University Hospital Rotterdam. All patients gave written, informed consent.

Radioactive Stent

The BX Isostent (^{32}P) (Isostent Inc), which is 15 mm in length and 3.0 or 3.5 mm in diameter, was used. The initial activity of the stents was measured and, thereafter, the date at which the radioactivity would have decreased to 6 to 12 μCi was calculated.

Procedure and Clinical Follow-Up

Procedural details have been published previously.[5] All patients received either 250 mg of ticlopidine BID or 75 mg of clopidogrel per day for 3 months after stent implantation and 80 mg of aspirin per day indefinitely. Revascularization was performed on the basis of clinical symptoms and/or evidence of ischemia on exercise testing. Clinical end points were death, Q-wave myocardial infarction, non–Q-wave myocardial infarction (creatine kinase-MB rise >2

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TABLE 1. Baseline Characteristics of the 22 Patients Studied

Male sex	20 (91)
Age, y	57 (38–73)
Risk factors	
Previous MI	12 (55)
Diabetes mellitus	3 (14)
Hyperlipidemia	18 (82)
Hypertension	9 (41)
Smoking	8 (36)
Family history	7 (32)
CCS class 3/4	15 (68)
Treated vessel	
LAD	12 (55)
LCx	5 (22.5)
RCA	5 (22.5)
Lesion type	
A	2 (9)
B1	10 (45.5)
B2	8 (36.5)
C	2 (9)
Lesion length, mm	10±3

Values are n (%), mean (range), or mean±SD. MI indicates myocardial infarction; CCS, Canadian Cardiovascular Society; LAD, left anterior descending coronary artery; LCx, left circumflex artery; and RCA, right coronary artery.

times normal upper limit), target vessel revascularization, non–target vessel revascularization, and early and late thrombotic occlusion of the target vessel.

Angiographic and IVUS Procedures

Angiography in multiple projections was performed before the procedure, after stenting, and at 6-month and 1-year follow-up. The stented vessel segments were examined with quantitative coronary angiography (CAAS II analysis system,[6,7] Pie Medical BV) and mechanical IVUS (CardioVascular Imaging System). IVUS images were acquired to coincide with the peak of the R wave by using an ECG-triggered pullback device with a stepping motor at 0.2 mm/step. This system eliminates the artifacts caused by the movement of the heart during the cardiac cycle.[8] The ECG-gated image acquisition and digitization was performed by a workstation designed for 3D reconstruction (EchoScan, Tomtec). A Microsoft Windows-based contour detection program was used for the volumetric 3D analysis.[8]

Core Laboratory Analysis Procedures

Quantitative coronary angiography using at least 2 orthogonal projections was performed. For analytical purposes, the following 3 regions of interest were defined: (1) stent, (2) target lesion, and (3) target vessel. The stent included only the radioactive stent. The target lesion was defined as the stent and 5 mm proximal and 5 mm distal to the edge. The target vessel was defined as the target lesion and the remaining segments of the treated vessel. Target lesion restenosis was defined as >50% diameter stenosis, located within the target lesion, at follow-up.[9] Edge restenosis was defined as >50% diameter stenosis, located at the proximal and/or distal edge, at follow-up.

Quantitative IVUS analysis of the stent and 5 mm proximal and distal to the stent was performed. Lumen and stent boundaries were detected using a minimum cost algorithm. Total stent and lumen volumes were calculated as previously described.[8] Neointimal volume was calculated as stent volume minus luminal volume. Feasibility, reproducibility, and interobserver and intraobserver variability of this system have been validated in vitro and in vivo.[8]

Statistical Analysis

Data are presented as mean±SD. Continuous data were compared using repeated measures ANOVA or a 2-tailed Student's *t* test as appropriate.

Results

Baseline demographics and lesion characteristics are shown in Table 1. Between 6 months and 1 year, target lesion revascularization and target vessel revascularization were performed in 4 patients (18%) and 5 patients (23%), respectively. No late occlusion was seen. No patient died or experienced myocardial infarction. In total, 21 of 40 patients (53%) were event-free through the 1-year follow-up.

Quantitative Coronary Angiography and IVUS Measurements

Quantitative coronary angiography data, presented as a subsegmental analysis of the stent area and the edges, are shown in Table 2. A significant decrease in the minimum and mean lumen diameters was noted between 6 months and 1 year (P=0.028 and P=0.001, respectively) compared with both edges. The late loss of mean lumen diameter was significantly larger after 6 months than before 6 months. Furthermore, in 11 patients (50%), the minimum lumen diameter at the edge at 6 months was detected within the stent at 1 year ("migration" from the stent edge to within the stent). Lesion progres-

TABLE 2. Subsegmental Quantitative Coronary Angiography Analysis

				Late Loss			
	Baseline	6 Months	1 Year	Baseline to 6 Months	6 Months to 1 Year	Total	*P* Between Periods
Minimum lumen diameter, mm							
Proximal edge	2.92±0.53	2.23±0.73*	2.08±0.50	0.69±0.80†	0.15±0.51‡	0.84	0.060
Stent	2.50±0.47	2.36±0.47*	1.93±0.52*	0.14±0.52†	0.43±0.56‡	0.57	0.16
Distal edge	2.29±0.61	2.17±0.58	2.08±0.49	0.36±0.49†	0.09±0.49‡	0.45	0.9
Mean lumen diameter, mm							
Proximal edge	3.19±0.56	2.73±0.57*	2.50±0.40*	0.39±0.62§	0.22±0.51‖	0.61	0.33
Stent	3.12±0.42	3.09±0.58	2.54±0.41*	0.03±0.62§	0.55±0.63‖	0.68	0.041
Distal edge	2.64±0.56	2.51±0.56	2.36±0.50	0.12±0.49§	0.16±0.52‖	0.28	0.9

*P<0.05, †P=0.0041, ‡P=0.025, §P=0.028, ‖P=0.001 by ANOVA.

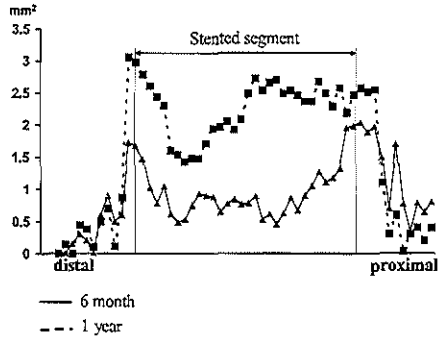

Figure 1. Mean neointimal area in stent at 6 months (■) and 1 year (▲) using IVUS.

sion to >50% diameter stenosis was observed in 5 patients. This was due to a progression of in-stent restenosis in 4 patients and a progression of a proximal stent-edge lesion in the other.

IVUS was completed in 19 patients; omissions were due to equipment failure[2] or patient clinical instability.[1] IVUS analysis demonstrated a significant increase in neointimal hyperplasia between 6 months and 1 year (18.16±12.59 mm^3 to 27.75±11.99 mm^3; increase of 52.8%; P=0.001), mainly in the mid and distal portions of the stent (Figure 1). An increase in neointimal hyperplasia >25% (range, 25% to 360%) occurred in 12 cases (63%), as shown in Figure 2. No change in lumen volume was noted at the stent edges between 6 months and 1 year.

Radiation Doses

The radioactive stents had a mean activity of 8.6±1.6 μCi at implantation and delivered 58±10 Gy to a depth of 1 mm from the stent at 100 days, with a dose rate of >15cGy/h. There was no correlation between stent activity or delivered dose and changes in minimum or mean lumen diameter at 6-month or 1-year follow-up.

Discussion

A worrying late progression of in-stent neointimal hyperplasia was observed between 6 months and 1 year after the implantation of radioactive stents, leading to target vessel or lesion reintervention in 5 of 26 patients (19%) who had been event-free at 6 months. The event-free rate at 1 year after the implantation of 6 to 12 μCi radioactive stents was 21 of 40 patients (53%), which compares poorly to the expected outcome after the implantation of a nonradioactive stent.[10]

In contrast to the tissue growth seen in malignancy, the DNA synthesis that occurs after nonradioactive stenting in experimental models terminates after 6 weeks.[11] At this time point, the activity of the radioactive stent used in this study would have been sufficient to inhibit cellular proliferation. Thereafter, the majority of lumen deterioration occurs in the first 3 months after conventional stent implantation, with minimal change between 6 months and 1 year,[12–14] and actual regression of neointimal hyperplasia between 1 and 3 years after stenting.[15] This latter phenomenon has been attributed to a reduction in the proteoglycan content of hyperplastic tissue.[16] Accordingly, the findings reported here of "breakthrough" or "rebound" hyperplasia causing further lumen deterioration between 6 months and 1 year must be interpreted as being specific to the effects of radioactivity, presumably due to a fall- off in radiation levels. The observation that the radioactive stent may provide a substrate for atherosclerosis may well have been predicted by Carter et al's porcine model.[17]

Because no significant stenosis progression was observed at the stent edges among our patients, the candy wrapper effect may be considered a short-term healing response to vessel wall injury beyond the stented vessel segment combined with the effects of low-dose radiation.[18,19]

Unexpected late luminal deterioration has also been reported between 6 months and 3 years among patients treated by catheter-based γ-radiation after repeat intervention for in-stent restenosis (mean loss of 0.37 mm with 4 of 17 patients [26%] progressing to restenosis [diameter stenosis >50%]), compared with no major changes in the placebo group.[4] The difference in the time frame of this virtual "rebound hyperplasia" between radioactive stenting and catheter-based γ-radiation therapy may be a function of the biological effects of and response to the type and dosage of radiation administered. Alternatively, late loss may also have

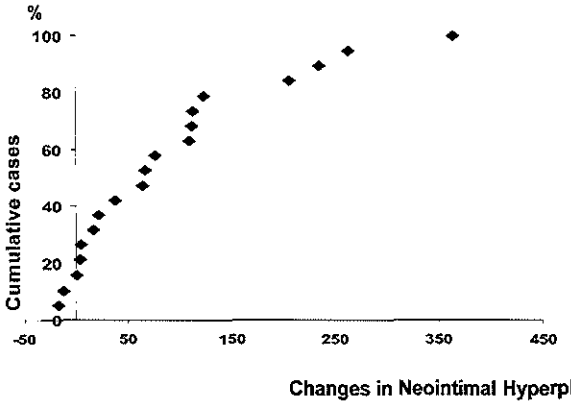

Figure 2. Cumulative distribution curve of percent changes in late neointimal growth after 6 months, as measured by IVUS.

occurred between 6 months and 1 year and remained subclinical in the catheter-based study.

Conclusions

Neointimal hyperplasia is delayed rather than prevented by radioactive stent implantation. The combination of this phenomenon of rebound hyperplasia with the established phenomenon of edge restenosis calls into question the clinical applicability of radioactive stenting using current approaches.

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Chapter 11

The black hole: echo-lucent tissue observed following intracoronary radiation.

Submitted.

The black hole: echo-lucent tissue observed following intracoronary radiation

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ABSTRACT

Background Recent trials in humans have given us insight into some of the consequences of intracoronary radiation. We describe a new observation noted on intravascular ultrasound (IVUS): that of intraluminal echo-lucent tissue, dubbed the 'black hole', noted at 6-month follow-up.

Methods and Results We analyzed 128 consecutive patients enrolled in brachytherapy protocols. The control group (C) consisted of individuals who underwent PTCA with (n = 48) and without (n = 22) stent implantation. Radiation groups included those who underwent low activity (LA) (n = 18), high activity (HA) (n = 26) and cold – end (CE) (n = 18) radioactive stenting. The Novoste Betacath (n = 39) and Guidant (n = 27) catheter-based radiation systems were also employed. At 6 – month follow – up echo-lucent tissue was identified in a total of 28 cases (22%). Angiographic restenosis occurred in 17 cases (61%). Of those lesions with restenosis echo-lucent tissue comprised 50% of the neo-intimal hyperplasia. No echo-lucent tissue was seen in the control group or in the LA group. HA and CE radioactive stents were most commonly associated with echo-lucent tissue (incidence 35% and 39% respectively). All occurred at the proximal or distal edges of radiation. Echo-lucent tissue was seen in all groups treated with catheter-based radiation with and without stenting. Atherectomy was performed on 4 lesions. Pathology demonstrated smooth muscle cells scattered in extracellular matrix containing abundant proteoglycans and an absence of elastin and mature collagen.

Conclusions This paper is the first to describe atherectomy samples extracted from humans after radioactive stent implantation. Also it is the first to link the IVUS finding of echolucency noted after intracoronary radiation with tissue rich in proteoglycans while poor in mature collagen and elastin

CONDENSED ABSTRACT

Using IVUS we describe an echo-lucent 'black hole' following intracoronary radiation. Radiation groups (n=128) included those who underwent radioactive stenting and catheter-based radiation. In total 28 'black holes' (22%) were identified (radioactive stents (>6.0μCi) =37%, catheter-based radiation =17%). Angiographic restenosis was a feature in 61% of these cases. Of those lesions with restenosis echo-lucent tissue was on average responsible for 50% of NIH. Atherectomy was performed on 4 lesions. Pathology demonstrated smooth muscle cells scattered in extracellular matrix containing abundant proteoglycans and an absence of elastin and mature collagen.

Key words: ultrasonics, radiation , proteoglycan.

ABBREVIATIONS

IVUS - intravascular ultrasound
μCi – microCurie
NIH – neointimal hyperplasia
SMC – smooth muscle cell

Intracoronary radiation, a therapeutic modality aimed at decreasing restenosis, has been investigated in both animals and humans for several years. With the advent of human trials we have started to understand the consequences of this treatment. These include non - healing dissection[1], late occlusion[2] and positive remodeling[3]. We describe a further new finding: an echo-lucent area within the lumen of the coronary artery, noted using intravascular ultrasound (IVUS). This phenomenon has been dubbed the 'black hole'. We describe the finding in terms of IVUS characteristics and present data on its incidence in various subgroups treated conventionally and with radiation. Finally we describe the pathological findings of this entity.

METHODS

We analyzed 128 consecutive patients enrolled in brachytherapy protocols, who had completed 6 - month follow-up that included angiography with IVUS. These protocols included individuals who had undergone catheter – based radiation using the ^{90}Sr / ^{90}Y Betacath™ (Novoste, Norcross, Ga) and ^{32}P Guidant (Santa Clara, CA) systems. The radioactive stent group comprised those who received 0.75 – 1.5μCi (n = 18), 6.0 – 12.0μCi (n = 26) and 'cold – end' (n = 18) stents (Isostent™ Inc., San Carlos, CA, USA). The control group included individuals who underwent PTCA with (n=48) and without stent implantation (n=22).

Catheter – based radiation

The Novoste Betacath and the ^{32}P Guidant β-radiation systems have been described in detail elsewhere [3,4]. We followed certain steps to ensure the correct identification and analysis of the irradiated segment post intervention and at 6 – month follow - up. First, an angiogram was performed after positioning the delivery catheter and the relationship between anatomical landmarks and the two gold markers were noted. Typically, the aorto-ostial junction and the side branches were used as landmarks. The landmark closest to either of the gold markers was used as a guide. During the motorized IVUS pullback, all side branches were counted and the guiding landmark was identified. The correct selection of the marker was confirmed by visualizing the position of the IVUS probe during a contrast injection. At follow-up, we selected the same region of interest and compared it with that after treatment.

Radioactive stent

The properties of low (0.75 – 1.5μCi) and higher activity (6.0 – 12.0μCi) radioactive stents and procedural characteristics specific to their implantation have been described elsewhere[5]. All stents were implanted with a stent to artery ratio of 1.1:1. 'Cold - end' stents were 27.3mm in length and available in diameters of 3.0 & 3.5 mm. The distal and proximal 5.7mm of the stent was non-radioactive, whereas the central 15.9mm had an activity of 3.0-24.0 μCi (see Figure 1).

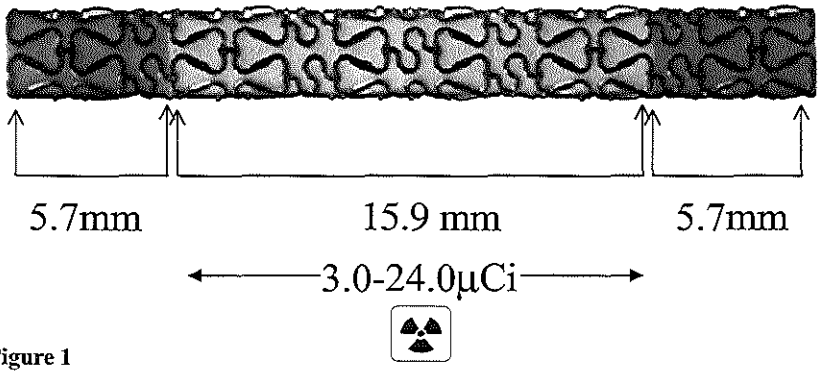

Figure 1
Cold-end stent with central radioactive segment and proximal and distal non-radioactive segments

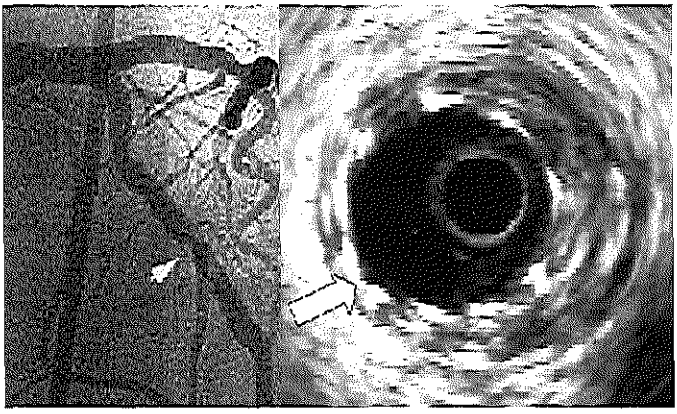

Figure 2
Left coronary angiogram performed at 6-month follow-up. Proximal in-stent restenosis is seen in a 6-12μCi stent implanted in the circumflex artery (left frame).
IVUS performed at 6 month follow-up demonstrating homogeneous black tissue from 6 to 1 o'clock (right frame).

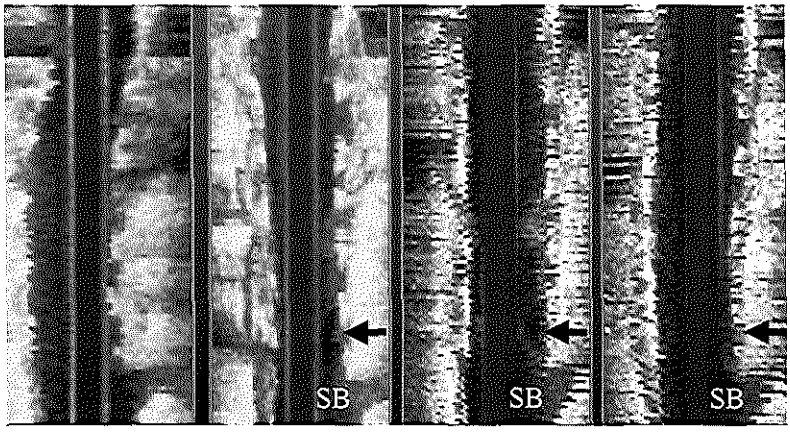

Figure 3
a. Baseline longitudinal IVUS reconstruction of freshly implanted stent.
b. Longitudinal reconstruction of the same transverse IVUS image seen in Fig 2. This

IVUS Acquisition

We used a mechanical 30MHz IVUS system (ClearView, CVIS, Sunnyvale, CA). Motorized pullback was performed at 0.5mm/sec. We examined the entire segment subjected to radiation, plus the associated 10mm proximal and distal edges. For radioactive stents this included 10mm proximal and distal to the final stent strut. Images were stored on S-VHS tape for later analysis. Findings were verified by 3 independent observers, who were blinded to whether images were from control or radiation cases.

IVUS definition of echo-lucent tissue

Lesions with the echo-lucent tissue had the following characteristics: a homogeneous black appearance without backscatter. Images with ring-down or other artefacts were excluded as were intraluminal echodense structures with associated attenuation. Exclusion of other causes of relative echolucency such as contrast[6], thrombus[7] or a lipid lake[8] was performed. Lesions were discrete and readily distinguishable from conventional neointimal hyperplasia (Fig. 2, 3). After radioactive stenting all lesions were observed adjacent to stent struts.

Definitions

The following dimensions were measured in each group: total vessel area (TVA), lumen area (LA), the area of echo-lucent tissue and the percentage of neointimal hyperplasia (NIH) caused by the echo-lucent tissue in the cross-section of greatest stensosis. Restenosis at 6–month follow-up was defined using standard angiographic criteria after off-line quantitative coronary angiography (diameter stenosis > 50%).

Medication

All patients received clopidogrel for between 1 month (conventional stenting) and 3-6 months (stenting plus catheter – based radiation or radioactive stenting), plus life-long aspirin.

Immunohistochemistry

For immunostaining, sections were preincubated with 0.3% hydrogen peroxide and Protein Block Serum-Free (X0909, Dako Corp, CA). A mouse monoclonal antibody against α-smooth muscle actin (1:5000 dilution, Dako) was used to identify smooth muscle cells. Polyclonal antibodies against biglycan (LF-51) and decorin (LF-122) were used for identification of proteoglycans (antibodies kindly provided as a gift from Larry Fisher, NIH, Bethesda, Maryland). Before incubating with proteoglycan antibodies, sections were first incubated with 1U/L chrondroitinase ABC (code #100332, Seikagaku Corp., Tokyo, Japan) for 15 minutes at 37°C to detach glycosaminoglycan side chains from the protein core; this procedure intensifies staining[9]. All primary antibodies were incubated overnight in a humidified chamber at 4°C. After rinsing in PBS, the primary antibody was labeled by a biotinylated link antibody directed against mouse using a

peroxidase based LSAB kit (Dako). Positive staining (brown reaction product) was visualized with a diaminobenzidine (Dako). After immunostaining, the sections were counterstained with Gill's hematoxylin, dehydrated in a graded series of alcohols, rinsed in xylene and mounted in Permount (Fisher Scientific).

RESULTS

At 6 – month follow - up 28 discrete areas of echo-lucent tissue ('black hole') (22%) were identified. No echo-lucent tissue was seen in the control group or in the low activity radioactive stent group. Angiographic restenosis was present in 61% of cases where echo-lucent tissue was present. Of those lesions with restenosis, echo-lucent tissue was on average responsible for 50% of neointimal hyperplasia. More severe stenosis was more frequently observed in the 6.0-12.0μCi and cold-end radioactive stent groups (mean stenosis = 63.1% ± 24.1) compared with catheter-based techniques (mean stenosis = 37.2% ± 20.5), p=0.005. Mean length of the echo-lucent tissue was 4.0mm ± 1.6mm (range 2-8mm).

Radioactive stent

Higher activity and cold-end radioactive stents were most commonly associated with echo-lucent tissue (Table 1). All occurred at the proximal and distal margins of radiation within the stent or at the stent edges. By definition this fall-off in radiation occurred in the final 1-2mm of 6.0-12.0μCi stents and in-stent for cold-end stents. Bilateral echo-lucent tissue was seen in 5 out of 7 cases that presented with restenosis 6 months after cold-end stent implantation. In four of theses cases the proximal edge was more severely affected.

Catheter-based

Echo-lucent tissue was seen in all groups treated with catheter-based radiation with and without stenting. These tended to be smaller lesions than those seen in the radioactive stent group (Table 1). After catheter-based radiation only one of the echo-lucent tissues described involved geographical miss (area of injury associated with a fall-off in radiation)[10].

Pathology features

Atherectomy was performed on 4 individuals (AtheroCath - Bantam™, DVI, Guidant, Temecula, CA, USA). Macroscopic assessment of the tissue samples showed two types of tissue: dark yellow, often containing pieces of stent strut and white more fibrotic appearing tissue (Fig. 4A). Microscopy revealed tissue containing smooth muscle cells in abundant extracellular matrix (myxoid change) with two distinct regions (Fig.4B, C) and containing abundant proteoglycans (Fig.4D). Region 1 (Fig 4E) was more cellular in nature, contained collagen and elastin (Fig 4C), and was not distinguishable from

	Location	% BHA of NIH	Restenosis (QCA)
Radioactive stent			
6-12 μCi (n=26)			
1	P edge	96	Y
2	P edge	100	Y
3	D edge	56	N
4	P edge	64	Y
5	P edge	100	Y
6	P edge	48	Y
7	D edge	71	Y
8	P edge	52	N
9	D edge	68	N
cold-end (n=18)			
10	P In stent*	100	Y
11	D In stent*	42	N
12	P In stent*	50	N
13	D In stent*	26	Y
14	P In stent*	48	Y
15	D In stent*	38	N
16	P In stent*	51	Y
Guidant CBS (n=16)			
17	In-stent	26	Y
18	In-stent	34	N
19	Out of stent	45	Y
Betacath CBS (n=18)			
20	In stent	48	N
21	In-stent	26	Y
22	In-stent	26	N
23	In-stent	56	N
Guidant: no stent (n=11)		%BHA of NIH	Restenosis
24		34	Y
25		90	N
Betacath: no stent (n=21)			
26		27	Y
27		16	Y
28		18	Y

CBS=catheter-based radiation plus stenting. P=proximal. D=distal. * at junction of radioactive and non radioactive segment of the stent. NIH=neointimal hyperplasia.

%BHA of NIH = % of NIH caused by echo-lucent tissue.

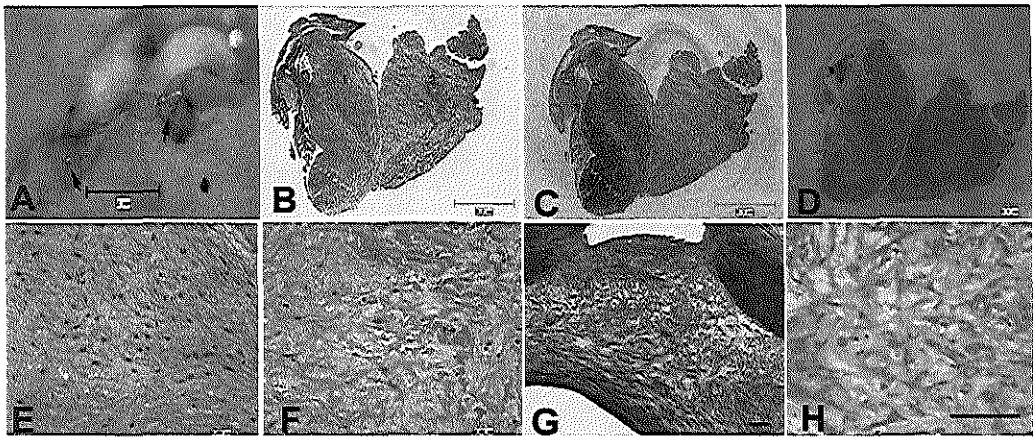

Figure 4

Fig. 4A Gross macroscopy of atherectomy specimen, showing that darker more yellow tissue overlies stent strut remnants (arrow), with a cover that is white in appearance.

Fig. 4B. Hematoxylin-Eosin stain showing two distinct regions; region 1 being more cellular than region 2.

Fig. 4C. Elastin stain, showing that region 1 consists of a more elastin and collagen rich tissue as compared to region 2.

Fig. 4D. Alcian Blue stain showing that the extracellular matrix contains large amounts of proteoglycans, most of which is hyaluronic acid (differential stain, not shown).

Fig. 4E. Detail of region 1, showing tissue that is similar in appearance to normal restenotic tissue.

Fig. 4F. Detail of region 2, showing sparse and pyknotic cells.

Fig 4G (Movat stain) and Fig 4H (H&E). Porcine model with 3μCi stent at 6 months. Extensive NIH consisting of SMCs in a proteoglycan matrix.

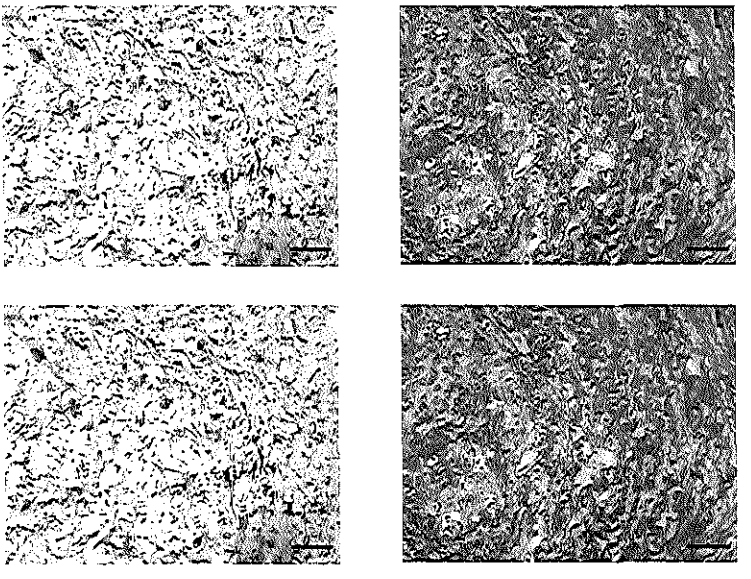

Figure 5

Fig 5A. Immunoperoxidase stained section showing a-actin positive smooth muscle cells.

Fig 5B. Immunoperoxidase stained section showing strong matrix positivity for biglycan.

normal restenotic tissue. Region 2 (Fig 4F) was more sparsely populated showing pyknotic nuclei, with some of the extracellular matrix having a coagulated or dense appearance (fibrinoid change). The latter was thought to be tissue constituting the echo-lucent tissue.

The area of the myxoid, proteoglycan rich matrix was thought to constitute the black hole. Three of the four biopsies were stained for a-actin (Fig 5A) to confirm presence of smooth muscle cells and for biglycan (Fig 5B), which is the dominant proteoglycan in restenotic lesions[9]. All three biopsies were strongly postive for biglycan and one biopsy stained for decorin was weakly positive.

DISCUSSION

Echo-lucent tissue ('black hole') noted at 6 – month follow-up was uniquely associated with intracoronary radiation. More common after radioactive stent (>6.0μCi) implantation, it was frequently located adjacent to the stent struts in areas of radiation fall-off, where it was associated with greater restenosis than the catheter-based techniques. Echo-lucent tissue may be a dominant cause of restenosis as seen in 4 patients (1,2,5 and 10). Overall it appeared to contribute to approximately 50% of the restenotic burden associated with NIH seen at 6-month follow-up. The lesion may be missed on IVUS examination due to its echolucency, caused by tissue rich in proteoglycans and poor in mature collagen and elastin.

What is unclear is the cause of such lesions. Certainly irradiation is associated with proteoglycan accumulation in various tissues[11,12]. Hehrlein has noted that the increase in neointimal volume in arteries treated with external beam radiation (EBR) was predominantly due to enhanced extracellular matrix production. This study suggested that the accumulation of extracellular matrix after stent deployment was augmented by external beam radiation and that excessive matrix formation was a determinant of failure of radiation therapy to prevent restenosis. The atherectomy samples of the current paper reflect changes seen in Carter's porcine model[12] with radioactive stents (Fig 2G & H). Carter has reported myxoid changes in low, intermediate and high activity stents (30%, 60% and 37% respectively) while no myxoid change was seen in control stents (personal communication, 2000). This would indicate that the echo-lucent tissue is a general response to irradiation of damaged vascular tissue.

The matrix seen is rich in biglycan proteoglycan; biglycan secretion by smooth muscle cells in culture has been shown to be controlled by TGF-β[13,14]. Therefore it is likely that radiation may induce greater TGF-β production that results in excessive biglycan production and formation of echo-lucent tissue on IVUS.

O'Brien[15] and colleagues suggest that biglycan may bind apoE and apoB in atherosclerotic intima. They also raise the possibility that apoE may act as a bridging molecule that traps apoA-I-containing HDL in atherosclerotic intima. Taken together these findings

are consistent with the hypothesis that biglycan may contribute to the pathogenesis of atherosclerosis by trapping lipoproteins in the artery wall.
Atherectomy samples taken at points where echo-lucent tissue is seen on IVUS shows aberrant nuclear morphology, suggesting ongoing cell death. This process continues to take place long after stent radioactivity has decreased to background levels. This indicates that radiation indeed has long-term effects. The presence of fibrinoid change may also be indicative of delayed healing, as was also seen in Carter's report.
With time the echo-lucent tissue becomes more discernible on IVUS due to its echodense cap (Figure 3). This cap is also seen on pathology showing collagen and elastin - rich tissue. This may be in keeping with a phenotypic change in the SMCs, allowing them to produce collagen and elastin - rich matrix typical of mature NIH with a lack of proteoglycan.

Conclusion

This paper is the first to describe atherectomy samples extracted from humans after radioactive stent implantation. Also it is the first to link the IVUS finding of echolucency noted after intracoronary radiation in various modalities with tissue rich in proteoglycans while poor in mature collagen and elastin

Limitations

Atherectomy was only performed in 4 patients and the findings described here will need to be substantiated with greater numbers. The issue of radioaction dosimetry is complex and fundamental, however is beyond the scope of this report.

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Chapter 12

Late Stent Malapposition Occurring after Intracoronary Beta-Irradiation Detected by Intravascular Ultrasound

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Late Stent Malapposition Occurring After Intracoronary Beta-Irradiation Detected by Intravascular Ultrasound

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ABSTRACT: We report a case of late stent malapposition occurring 6 months after intracoronary beta-irradiation detected by three-dimensional intravascular ultrasound, in spite of good apposition immediately after the procedure. Volumetric quantification revealed that stent volume remained unchanged, whereas total vessel volume increased by 13% after 6 months within the stent area. The increase of the vessel volume took place mainly in the proximal part of the stent, where the malapposition was located.

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Key words: angioplasty, brachytherapy, intravascular ultrasound, vessel remodeling

Experimental studies have shown that endovascular radiation reduces neointima formation.[1-3] In humans, three randomized trials have reported a reduction in restenosis rate after successful reintervention followed by intracoronary brachytherapy for the treatment of in-stent restenosis.[4-6] Early safety of this new therapy has been demonstrated.[7-9] Although 2- and 3-year follow-up of patients treated with gamma-radiation has been reported,[10,11] long-term safety of radiation has been questioned.[12]

In humans, radiation has been shown to prevent vessel shrinkage,[13] inhibit neointimal formation,[4,5] or induce vessel enlargement that eventually accommodates an increase in plaque.[14] The importance of vessel enlargement in patients receiving stents has not been investigated.

We report a case of late stent malapposition occurring 6 months after intracoronary beta-irradiation demonstrated by three-dimensional intravascular ultrasound (IVUS), in spite of good apposition immediately after procedure.

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Case report. *A 60-year-old male with Canadian Cardiovascular Society class III angina pectoris was referred to our institution for percutaneous transluminal coronary angioplasty (PTCA). Coronary angiography revealed a severe stenosis in the proximal segment of the left anterior descending coronary artery (LAD) (Figure 1A). Quantitative coronary angiography (QCA) was performed off-line (CAAS II system, Pie Medical, Maastricht, The Netherlands). Lesion length measured 14.9 mm, minimal luminal diameter (MLD) 1.20 mm, reference vessel diameter 3.10 mm, and percentage of diameter stenosis 61%. Although he had a previous myocardial infarction, left ventriculography revealed no hypokinesia with an estimated ejection fraction of 54%.*

Strategy. *The patient was enrolled in a study to evaluate safety and efficacy of beta-irradiation following PTCA using the Guidant Intravascular P-32 Radiotherapy System (Guidant Corporation Vascular Intervention, Houston, Texas).[15] The Medical Ethics Committee of the University Hospital Dijkzigt approved the use of intracoronary radiation, and the patient has given written informed consent. The strategy was to perform a*

Table 1. IVUS volumetric 3-D reconstruction analysis

	Baseline	Follow-up	Difference
Lumen volume (mm^3)	179.7	188.1	+8.4
Stent volume (mm^3)	179.7	181.1	+1.4
EEM volume (mm^3)	351.8	402.6	+50.8
Plaque volume (mm^3)	172.1	214.5	+42.4
Mean lumen area (mm^2)	9.9	10.5	+0.6
Mean stent area (mm^2)	9.9	10.1	+0.2
Minimum lumen area (mm^2)	7.8	8.0	+0.2
Mean EEM area (mm^2)	19.4	22.1	+2.7
Minimum EEM area (mm^2)	18.3	18.5	+0.2

EEM = external elastic membrane

direct stent deployment without pre-dilatation followed by irradiation of the target segment. The Source Delivery Unit is a computer-controlled, source wire-handling device that delivers localized beta-radiation to a coronary artery at 0.5 mm into the vessel wall.[12] The radiation dose was randomly assigned to the patient. The Guidant P32 Source Wire is a 0.018" guidewire with a 27-mm long beta-emitting source in its tip. The Centering Catheter is a multi-lumen, spiral-designed balloon catheter with a rapid-exchange tip, designed to operate using 4 atmospheres of pressure (Figure 1B).

Procedure. *The left coronary artery was cannulated with a Judkins left 8 French (Fr) guiding catheter (Cordis Corporation, Warren, New Jersey) using the standard femoral approach. The lesion was crossed with a 0.014", 315-cm long Hannibal® wire (Schneider, Bülach, Switzerland) which was placed distally in the LAD. Subsequently, a 3.5 x 18 mm Multi-Link® stent (Guidant Corporation, Santa Clara, California) was directly implanted. A balloon post-dilatation of the target lesion was performed using a 4.0 x 15 mm Tacker® balloon (Cordis, Miami, Florida) inflated to 14 atmospheres. IVUS images were then obtained using a 2.9 Fr mechanical ultrasound catheter operating at 30 MHz (CVIS, Sunnyvale, California). The size of the centering balloon was chosen based on mean vessel reference diameter (mean of proximal and distal reference diameter) defined by IVUS. A 3.05 mm centering balloon was then placed over the wire at the target site. The radiation sources remained at the treatment site in order to deliver a prescribed dose of 4200 cGy at 0.5 mm into the vessel wall (Figure 1B). The delivery unit based on mean reference vessel diameter automatically calculates the dwell time. After intracoronary irradiation, an ECG-gated IVUS pullback at 0.2 mm/step was performed with the same system. The stent was well-apposed with a minimal lumen area (MLA) of 7.8 mm^2 (Figure 2C). No edge tear was detected by IVUS. QCA revealed a MLD of 2.79 mm,*

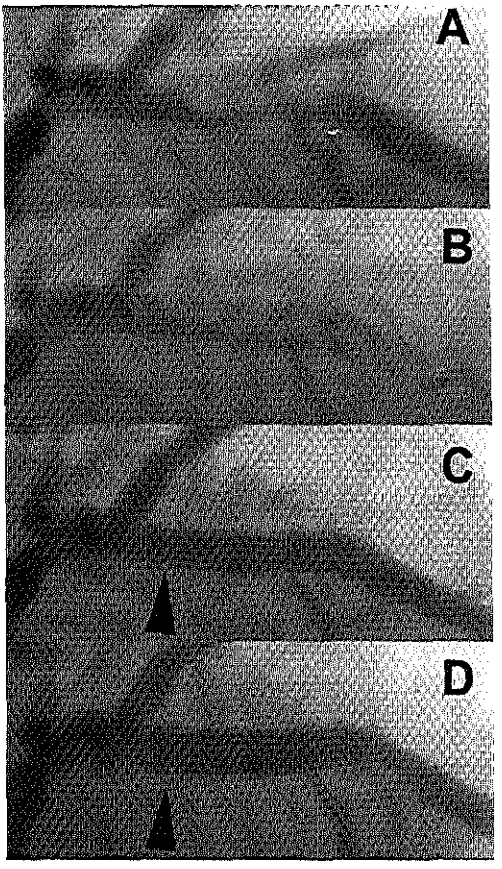

Figure 1. (A) *Pre-procedure angiogram shows the stenosis in the proximal segment of the left anterior descending artery;* (B) *centering balloon inflated during irradiation;* (C) *post-procedure angiogram (arrowhead indicates the location where stent malapposition appeared at follow-up);* (D) *6-month follow-up angiogram (arrowhead indicates the stent malapposition site).*

located at the proximal portion of the stent, and residual percentage stenosis of 16% (Figure 1C). The patient's hospital stay was uneventful and he was discharged 2 days after the procedure on aspirin (250 mg/day) and ticlopidine (250 mg twice a day for 15 days). Six months later, the patient returned to the catheterization laboratory for angiographic and IVUS control as part of the protocol. The patient had no complaints and the stress test was negative. The angiogram (QCA) revealed no signs of restenosis (Figure 1D) with an MLD of 2.34 mm, located outside the stent, and a diameter stenosis of 33%. Luminal diameter at the site of malapposition was 2.98 mm. Six-month IVUS images, using the same system, revealed no neointimal formation throughout the stent. However,

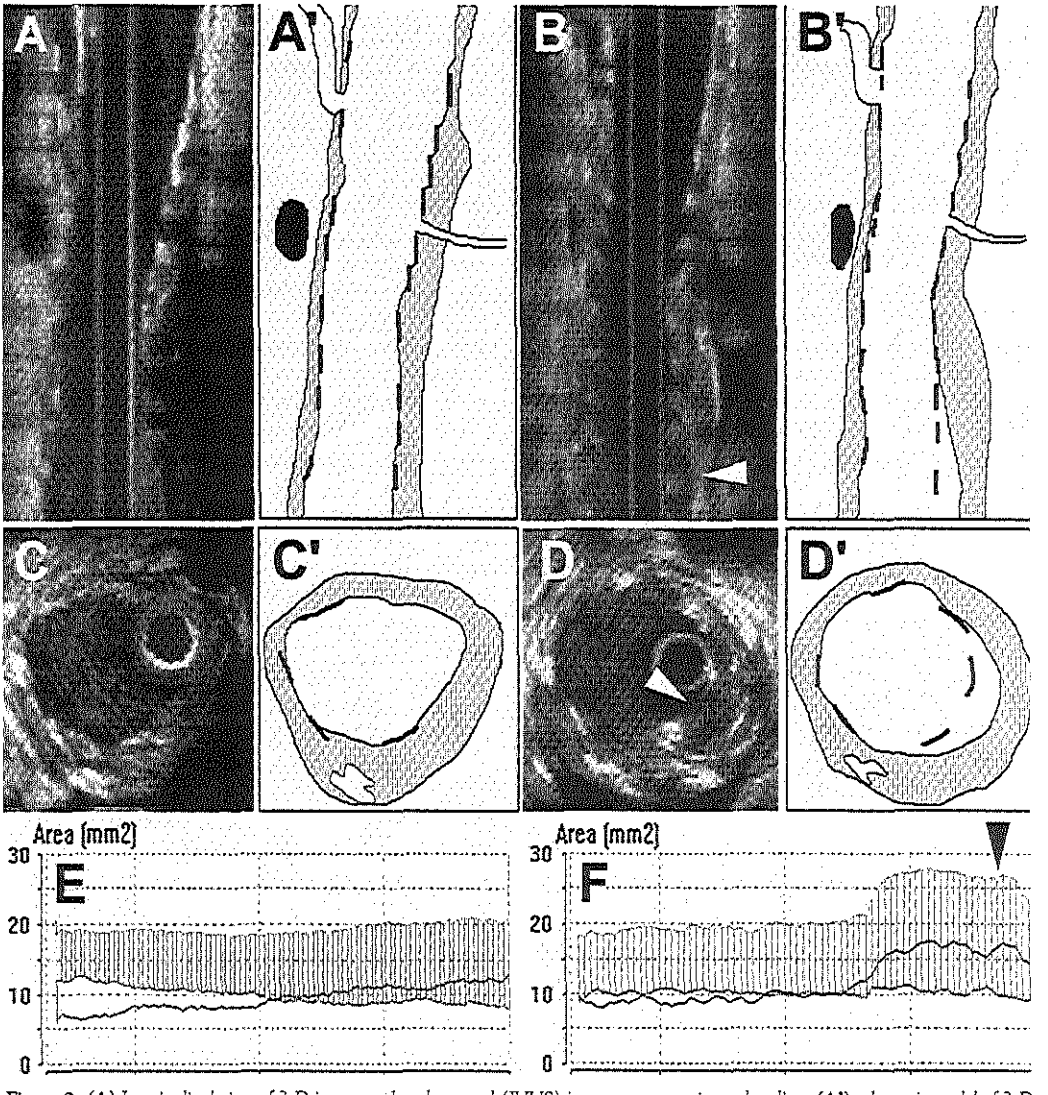

Figure 2. *(A) Longitudinal view of 3-D intravascular ultrasound (IVUS) image reconstruction at baseline; (A') schematic model of 3-D IVUS image reconstruction at baseline; (B) longitudinal view of 3-D reconstruction IVUS image at follow-up (arrowhead indicates the malapposition site); (B') schematic model of 3-D reconstruction IVUS image at follow-up; (C) post-procedure IVUS cross-sectional image at the site where stent malapposition appeared at follow-up; (C') schematic model of IVUS cross sectional image at baseline; (D) IVUS cross-sectional image at follow-up (arrowhead indicates a space behind the stent at 2–5 o'clock — stent malapposition); (D') Schematic model of IVUS cross-sectional image at follow-up; (E) graphic of external elastic membrane (EEM) and stent areas at baseline (upper line: EEM area, lower line: stent area); (F) graphic of EEM area and stent area at follow-up (upper line: EEM area, lower line: stent area) (arrowhead indicates the local EEM area increase from nearly 20 mm² to more than 25 mm²).*

a malapposition of the proximal end of the stent without compromising the lumen was observed (Figure 2D) by IVUS. Contrast injection filled the cavity behind the stent, confirming the presence of malapposition during IVUS imaging. Based on clinical status, no further intervention was performed.

Intravascular ultrasound measurements. *All IVUS images were analyzed off-line by 3 investigators in a "blind" approach. An ECG-gated image acquisition and digitization workstation (EchoScan, TomTec, Munich, Germany) was used for three-dimensional IVUS image reconstruction. Volumetric quantification*

was performed by means of a Microsoft Windows®-based contour detection program developed at the Thoraxcenter.[16] This program constructs two longitudinal sections from the data set and identifies the contours of the lumen, media and stent boundaries. Ninety-four planar cross-sections of the stented segment were carefully checked and edited by 2 cardiologists. The feasibility and intra- and inter-observer variability of this system have been previously reported.[17,18] The reproducibility of measurements of the external elastic membrane (EEM) in stented segments has been also demonstrated.[19]

The results of two-dimensional and three-dimensional analysis are shown in Table 1, Figure 2E, and Figure 2F. Total vessel volume increased by 51 mm³ (13%) after 6 months, parallel to an increase in plaque volume of 42 mm³ (20%). However, the magnitude of the plaque in growth was not sufficient to completely fulfill the gap left between stent struts and vessel wall. The calculated difference was 7 mm³. No neointimal formation was found in the malapposed stent site, which revealed a lumen CSA of 8.0 mm² (Figure 2D). The increase of the vessel volume took place mainly in the proximal part of the stent, where the malapposition is located (Figure 2F). Stent volume of the proximal enlarged segment (6.9 mm in length) remained similar (61 mm³ at baseline versus 68 mm³ at 6 months), whereas total vessel volume increased from 140 mm³ to 179 mm³ after 6 months. The stent malapposition was also demonstrated on the longitudinal view of the three-dimensional reconstruction (Figure 2).

Discussion. This is the first case report which demonstrates an unexpected late (at 6 months) stent malapposition after intracoronary radiotherapy revealed by three-dimensional IVUS, despite the good apposition of the stent post-procedure. Volumetric analysis demonstrated a vessel enlargement without a concomitant increase or decrease in the stent volume.

Stent malapposition has been related to an increased risk for subacute thrombosis.[20] Thrombotic events late after stenting followed by radiation have been recently reported.[12,21] However, the relationship between late thrombosis and stent malapposition late after brachytherapy remains to be elucidated in large IVUS studies.

Meerkin et al. demonstrated that EEM area did not change during the follow-up period after beta-radiation.[13] However, the analysis of single planar cross-sectional images may have underestimated the possibility of positive vascular remodeling in their study. On the other hand, a volumetric three-dimensional IVUS study has demonstrated that radiation promotes positive vessel remodeling by showing an increase of the EEM volume (40 mm³) at 6 months after intracoronary beta-radiotherapy.[14] In addition, Condado et al. have reported on the occurrence of coronary aneurysm formation, which illustrates an exaggeration of vessel remodeling after high doses of gamma brachytherapy.[11] In this case, we also observed an enlargement of the total vessel volume (51 mm³).

Although some previous reports showed acute recoil of the Palmaz-Schatz stent,[22-24] tubular stents are not believed to recoil or expand chronically.[23-25] Thus, the Multi-Link stent used in this case is not expected to change its volume after 6 months.[26] Then, considering the inability of self-expansion of a rigid tubular stent, the increase of the total vessel volume may play an important role in the mechanism of stent malapposition formation late after the treatment. The use of self-expandable stents in the setting of intracoronary radiotherapy may be an alternative to avoid this problem due to their ability to expand chronically.[27]

Besides vessel enlargement, we should also consider the possibility of tissue or non-cellular structure (thrombus or lipid lakes) occupying the space behind the stent after the procedure. Such structures may not be detected by post-stenting IVUS and may diminish after 6 months. The "killing" effect of radiation (necrosis or accelerating apoptosis) and dissolution, disruption or embolization of these non-cellular structures may play a role in this phenomenon. These hypotheses should be further investigated by large population studies.

In conclusion, this report illustrates an unexpected finding following coronary stenting: late stent malapposition. Whether this finding is related to the combination of radiation and stent placement remains to be elucidated. Further studies with serial IVUS analyses should be performed in order to elucidate the pathophysiology and clinical impact of this finding.

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Summary and Conclusions

Intracoronary Brachytherapy
What have we learnt from our personal experience?

Interventional cardiology is a rapidly growing field in medicine. Most new treatment developments have been defined by large multicenter randomized trials in the name of 'evidence-based medicine'. In the field of intracoronary brachytherapy, most of the information provided by these trials is related to the use of catheter-based γ-radiation for in-stent restenosis. In Europe, most of the experience and mechanistic information in this field have been obtained from the treatment of de novo lesions using β-radiation. Consequently, the perception of the bright and dark sides of this new treatment modality might be slightly different, or at least perceived in a different manner.

In this thesis, changes in vessel morphology were investigated in both the bright and dark spectrum of the results with this mode of therapy. The first chapter is an overview of intracoronary brachytherapy.

In chapter 2, the feasibility of intracoronary brachytherapy is presented. Although, the procedures for brachytherapy are more complicated than the balloon angioplasty and stenting, we demonstrated the high success rates of brachytherapy in the daily practice of interventional procedures. Subsequently, chapters 3 and 4 present the main mechanisms for preserving the lumen after catheter-based intracoronary radiotherapy. Plaque growth was observed in the irradiated and non-irradiated segments as well as both in the central and edge parts. The difference between the radiation group and non-radiation group was found to be the degree of vessel remodeling rather than the inhibition of tissue proliferation. Similar behavior was also demonstrated between stenting and balloon angioplasty when the vessel was irradiated, although the stent is supposed to be beneficial for the prevention of restenosis. This finding may be interesting in order to clarify the effects of radiotherapy. In chapter 5, tensile stress, one of the biophysical factors affecting vessel wall morphology, was introduced to show the concept of biophysical factors and their contribution to the restenosis process. The most interesting finding of this study was that a higher radiation dose (>6 Gy) delivered to the adventitia eliminates the effect of tensile stress, which may suggest the presence of mechanoreceptors in the vessel wall and their abolition by the radiation. QCA methodology for the evaluation of catheter-based radiotherapy was used and the data

are presented in chapter 6. Because of more frequent migration of the MLD after intracoronary radiation, specific segments need to be reported to assess the effect of intracoronary brachytherapy. IVUS may be necessary to assess the vessel remodeling induced by intracoronary radiotherapy. However, it is important to note that clinical decisions are usually made according to angiographic results of entire vessel segments. Therefore, in chapter 7, the validity of QCA to detect vessel remodeling was investigated since positive vessel remodeling is frequent after balloon angioplasty followed by intracoronary radiation.

In the second part, unexpected phenomena observed in the clinical trials studying the effect of brachytherapy are reported. Although intracoronary brachytherapy is a powerful and increasingly applied therapy to prevent restenosis, several limitations and complications that limit the application of this mode of therapy need to be investigated and solved. In chapter 8, the so called "edge effect" was investigated for the first time using a specific QCA methodology. Combination of low-dose radiation and injury induced by balloon or stent was responsible for the higher lumen loss and higher restenosis rate than expected at the edges of the irradiated segments in the setting of catheter-based β-radiation. The term "geographical miss" was introduced from radio-oncology to define that the cause of this treatment failure was due to the inappropriate radiation dose on the injured segments. In chapter 9, we report the long-term follow-up of patients treated with catheter-based β-radiation. In this study, considerable occurrence of myocardial infarction after 6 months was observed mainly due to thrombotic occlusion of the target vessel. Delayed healing as a result of the radiation is thought to be the principal cause of this phenomenon. Although long-term antiplatelet therapy (more than 2 years) may solve this problem, target vessel revascularization rates (comparable to the balloon arm of BENESTENT trial) were higher than expected. The study presented in chapter 10 demonstrates a delayed restenotic response after radioactive stenting. Lumen loss occurred more after 6 months than before 6 months within a stent, while the vessel lumen remained unchanged after 6 months at the stent edges. This finding may suggest that restenosis could be delayed for the period of time necessary for the population of smooth muscle cells to regenerate by using a lower radiation dose. Specific IVUS findings at follow-up of patients receiving brachytherapy was coined "Black hole" by one of our experienced technicians. Proteoglycan rich extracellular matrix was observed in the specimens of the "black hole" sites obtained by atherectomy. Half of the lesions that had "black hole" developed restenosis. This new finding and its possible genesis is reported in Chapter 11. In chapter 12, late stent malapposition which is one of the consequences of vessel remodeling is reported. This complication may result in the presence of bare stent material for a long time. This finding may also be a factor which causes late thrombosis after β-radiation.

Intracoronary brachytherapy is an evolving therapy to prevent restenosis after percutaneous coronary intervention, particularly for the patients with in-stent restenosis.

However, potential benefits and adverse effects of radiation still remain to be investigated in specific clinical trials, since the occurrence of restenosis currently reported in clinical trials appears to be higher than expected. The restenotic process after radiation is very complex and remains poorly understood. The studies reported in this thesis addressed some of these factors which may help to elucidate its specific mechanisms and have raised several problems of intracoronary radiation. Further investigations may help this therapy to develop into one of the standard procedures in interventional cardiology.

Samenvatting en conclusies

Intracoronaire brachytherapie
Wat hebben we geleerd van onze persoonlijke ervaring?

De interventiecardiologie is een snel groeiend vakgebied in de geneeskunde. De meeste nieuwe ontwikkelingen zijn omschreven door grote gerandomiseerde multicentra onderzoeken. Op het gebied van intracoronaire brachytherapie is de meeste informatie, verkregen door deze onderzoeken, gebaseerd op het gebruik van catheter-gebaseerde gamma bestraling voor de behandeling van in-stent restenose. In Europa is de meeste ervaring en begrip van werkingsmechanisme in dit gebied verkregen voor de behandeling van de novo lesies met beta bronnen. Daaruit volgend kunnen de perceptie van de lichte en donkere zijden van deze nieuwe technologie iets anders zijn, of op zijn minst op een andere manier waargenomen zijn.

In dit proefschrift zijn de veranderingen in vaatmorfologie onderzocht in zowel de lichte als de donkere zijden van deze behandeling. Het eerste hoofdstuk toonde een overzicht van de intracoronaire brachytherapie.

In hoofdstuk 2 werd de toepasbaarheid van intracoronaire brachytherapie voor de dagelijkse praktijk gepresenteerd. Alhoewel brachytherapie procedures nog steeds moeilijker zijn dan de gebruikelijke ballon angioplastiek en stent implantatie, toonde dit hoofdstuk aan dat brachytherapie een hoog succespercentage heeft in de dagelijkse praktijk. Hoofdstukken 3 en 4 demonstreerden vervolgens de voornaamste mechanismen voor het behouden van lumen na catheter-gebaseerde radiotherapie. Plakgroei werd waargenomen in zowel de bestraalde als de niet-bestraalde segmenten, en ook in zowel de centrale als de randen gedeeltes. Het verschil tussen de bestraalde en de niet-bestraalde groep bleek meer te berusten op de graad van vaat remodelering dan op de inhibitie van weefselproliferatie. Een vergelijkbaar resultaat werd ook gedemonstreerd tussen stent implantatie en ballon angioplastiek indien het vat vervolgens werd bestraald. Deze vondst kan erg interessant zijn om het werkingsproces van de radiotherapie te verduidelijken. In hoofdstuk 5 werd de spanningsstress (tensile stress), een van de biofysische faktoren, welke een effekt heeft op de vaatwand morfologie, geïntroduceerd om het concept van biofysische faktoren en hun contributie aan het restenose proces aan te tonen. De meest interessante waarneming van deze studie was dat een hogere bestralingsdosis (>6 Gy) bezorgd op de adventitia het effect van de spanningsstress

elimineert, hetgeen mogelijk suggereert dat er mechanoreceptoren op de vaatwand bestaan, welke geëlimineerd worden door radiotherapie. Een nieuwe QCA methodologie werd voorgesteld voor catheter-gebaseerde radiotherapie in hoofdstuk 6. Omdat er vaker een relokatie van de MLD optreedt, moeten specifieke segmenten gerapporteerd worden om het effekt van intracoronaire brachytherapie vast te stellen. In hoofdstuk 7 werd de validiteit van de QCA om vaatremodelering vast te stellen onderzocht, aangezien positieve vaat remodelering frequent optreedt na ballon angioplastiek gevolgd door intracoronaire bestraling. IVUS zou noodzakelijk kunnen zijn om vaat remodelering, veroorzaakt door intracoronaire radiotherapie, vast te stellen. Het is echter belangrijk te vermelden dat klinische beslissingen meestal plaatsvinden aan de hand van de angiografische resultaten van de segmenten van het vat.

In het tweede gedeelte werd een onverwacht fenomeen gerapporteerd, welke werd waargenomen in de klinische studies. Alhoewel intracoronaire brachytherapie een krachtige behandeling is voor de preventie van restenose en steeds vaker wordt toegepast, zijn er verschillende complicaties en bevindingen, die deze behandeling beperken, welke onderzocht en opgelost dienen te worden. In hoofdstuk 8 werd het randen effect (edge effect) voor de eerste keer onderzocht met een specifieke QCA methodologie. Een combinatie van een lage bestralingsdosis en vaatwandbeschadiging door een ballon of stent was verantwoordelijk voor een hoger dan verwacht lumen verlies en restenose percentages aan de randen van de bestraalde segmenten in het kader van catheter-gebaseerde beta bestraling. De term "geographical miss" van de radio-oncologie werd geïntrodoceert om te omschrijven dat de oorzaak van dit falen van de behandeling veroorzaakt werd door een inadequate bestraling van de beschadigde segmenten. Hoofdstuk 9 rapporteerde de lange termijns resultaten van patiënten behandeld met catheter gebaseerde beta bestraling. Een flink aantal myocardinfarcten werden waargenomen 6 maanden na bestraling, welke voornamelijk veroorzaakt werd door een thrombotische occlusie van het bestraalde vat. Een vertraagde genezing ten gevolge van de bestraling lijkt de voornaamste veroorzaker van dit fenomeen te zijn. Alhoewel anti-plaatjes behandeling gedurende een lange tijd (> 2 jaar) dit probleem zou kunnen oplossen, is de vaat revascularisatie percentage van het behandeld vat (in vergelijking met de ballon tak van de BENESTENT studie) hoger dan verwacht. In hoofdstuk 10 werd een vertraagde restenotische response na het plaatsen van een radioactieve stent waargenomen. Lumen verlies in de stent tradt vaker op na meer dan 6 maanden na stent implantatie, dan in de eerste 6 maanden na stent implantatie. Het lumen verlies aan de randen daarentegen bleef ongewijzigd na 6 maanden. Dit kan suggeren dat de applicatie van een lage bestralingsdosis de restenose alleen zou vertragen voor de tijdsperiode dat de populatie van gladde spiercellen nodig heeft om te regenereren. Het "zwarte gat" werd beschreven door onze ervaren technicus voor een specifieke IVUS waarneming bij de follow-up van brachytherapie. Proteoglycaanrijke extracellulaire matrix werd waargenomen in monsters van "zwarte gaten" gebieden, welke verkregen werden door

atherectomie. De helft van de lesies, welke "zwarte gaten" hadden, ontwikkelden zich later in restenose. Deze nieuwe vondst werd gerapporteerd in hoofdstuk 11. In hoofdstuk 12 wordt een van de consequenties van vaat remodelering gerapporteerd, te weten late stent malappositie, welke kan resulteren in het bestaan van blootgelegde staal gedurende lange tijd. Dientengevolge kan deze vinding gerelateerd zijn aan de late thrombose na bestraling.

Intracoronaire brachytherapie is een robust en progressieve therapie ter preventie van restenose na een percutane coronaire interventie. Potentiële voordelen en bijwerkingen van bestraling dienen echter nog steeds onderzocht worden in klinische protocollen, aangezien restenose vaker dan verwacht voorkwam in klinische studies. Het restenose proces na bestraling is erg complex en moet nog opgehelderd worden. Dit proefschrift kaartte enkele van deze faktoren aan en heeft verschillende problemen van intracoronaire brachytherapie aan het daglicht gebracht. Ik hoop dat deze onderzoeken er toe kunnen bijdragen dat deze bestralingsbehandeling zich kan ontwikkelen tot een van de standaard behandelingen in de interventiecardiologie.

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