Unravelling of Restenosis:
Understanding the Mechanism and Finding a Solution.
Implications of IVUS-3D and Brachytherapy

Restenose: Een zoektocht naar de
ontstaansmechanismen en behandelingsmogelijkheden.
Toepassingen van 3-dimensionele IVUS en intracoronaire brachytherapie

Proefschrift

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To Érica ,
our baby,
my parents,
and God.

CONTENTS

Introduction

Overview of the Thesis

The purpose of this thesis was twofold; firstly, to assess the pathophysiology of restenosis following percutaneous transluminal coronary angioplasty (Part I); secondly, to explore the potential of a novel technique, intravascular beta-radiation therapy, to prevent the recurrence of coronary stenosis after percutaneous treatment (Part II).

The first part of this thesis represents an attempt to add further insights into the complex mechanism of restenosis. As will emerge in this first section, our hypothesis has been that vessel remodeling, watched as a continuous process, will ultimately determine lumen loss after balloon angioplasty but not after stents. The pathophysiology of restenosis was addressed in the second chapter, which describes the relationship between inflammation, i.e. activated neutrophils, and angiographic lumen renarrowing after coronary stenting and balloon angioplasty.

In the third chapter, the local vascular response to balloon injury was assessed by means of sub-segmental analyses of the entire target coronary segment using three-dimensional intravascular (IVUS) reconstruction. This chapter also introduces a new methodology to investigate the magnitude and mechanism of the restenotic process by assessing this phenomenon at the site of maximal lumen loss, which actually represents the location of maximal arterial wall response to injury.

In chapter 4, neointimal proliferation and potential stent recoil (remodeling) were assessed in coronary segments treated with two second-generation tubular stents using three-dimensional IVUS volumetric quantification of the entire injured segment. As three-dimensional IVUS imaging is the most refined technology currently available, it has also been applied in the second part of the thesis (chapters 8-10, 12), which assesses the vascular wall response to intravascular radiation therapy; an emerging therapeutic modality to prevent restenosis.

In the chapter 5, we described recent clinical applications of intracoronary radiation therapy. New methodological and procedure-related concepts mainly derived from the vascular effect of this new therapy are described in chapters 6 and 7.

In chapters 8 to 10, morphological changes of vessel structures after intracoronary radiation therapy using either catheter-based systems or radioactive stent were assessed. Special attention has been given to vascular remodeling, which appeared to be highly influenced by radiation. Also, the "edge-effect" phenomenon, i.e. lumen loss observed in the edge of the irradiated segment, has also been explored in chapters 7 (by means of quantitative coronary angiography), 9 and 10 (by means of three-dimensional IVUS analysis).

Finally, the potentially deleterious effects of this new therapy have been critically analyzed in the last 3 chapters (11-13). These chapters report an alarmingly high incidence of sudden coronary occlusion late after intravascular radiation therapy (chapter 11), and intriguing IVUS findings occurring late (6-month follow-up) after treatment, late stent malapposition (chapter 12) and persisting unhealed dissection (Chapter 13).

CHAPTER 1

Restenosis: the problem and how to deal with it

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Introduction

Facing the new millennium, the costly problem of restenosis after percutaneous transluminal coronary angioplasty (PTCA) remains unresolved. Indications for angioplasty as well as the number of percutaneous interventions performed each year[1] have been expanded considerably since the early days. In 1994, a total of 224.722 coronary angioplasty (PTCA) procedures were reported in Europe, an increase of 52% compared with 1992[2], and the latest European statistics estimates that the annual need for PTCA is 739 per million inhabitants[3] In view of these consideration, clinicians may realize why researchers are spending so much time and money in attempts to finding a solution for this "iatrogenic disease" originated from the geniality of et al[4]. The aim of this chapter is to summarize the current data regarding pathophysiology and prevention and/or treatment of restenosis.

Pathophysiology of Restenosis

The biological aspects of restenosis are much too complex for a clinical article; thrombosis, inflammation, smooth muscle cell (SMC) migration/proliferation and extra-cellular matrix formation/degradation represent the fundamental sequence of healing and ultimately lumen reduction after catheter-based vascular intervention [5-11]. The interplay between these factors is coordinated by multiple intra- and extra-cellular elements (growth factors, cytokines, hormonal factors, nitric oxide, protein kinases, etc)[10, 12]. Local mechanical stimuli, chronic shear and/or tensile stress[13 14, 15], may further influence the restenotic process.

Based on experimental studies, platelet aggregation and thrombus formation have been suggested as the foremost process leading to restenosis[7, 8, 16, 17]. At the site of injury, platelet aggregation, so-called white thrombus, may represent the major source for attractants and mitogens for smooth muscle cells. The platelet derived growth factor (PDGF), which may also be secreted by endothelial cells and macrophages, has been considered as the major promoter of SMCs migration[18-21]. In addition, thrombin may stimulate SMC proliferation[22] and precipitate endothelial dysfunction[23]. The hypothesis that thrombus represents the core of the restenotic process has been supported by studies using angioscopy providing clinical evidence of early thrombus formation after PTCA[24, 25].

Inflammation has also been implicated with restenosis, since leukocytes have been found early and abundantly at the site of vascular injury[26-28]. The inflammatory cell component of the restenotic process appears to play a greater part following stent (foreign body) implantation than balloon angioplasty[29-32]. Whether the association between enhanced inflammatory response and vessel enlargement, as observed in a recent experimental study[33], represents a potential beneficial effect of inflammation[34] on vessel remodeling remains to be elucidated.

The smooth muscle cell has long been implicated in the restenotic process[35, 36] due to its ability to migrate, proliferate and synthesize extra-cellular matrix upon stimulation[20, 29, 37-41]. After shifting from the contractile to the synthetic phenotype, SMCs may proliferate from 24h to 2-3 months after vascular injury, returning to the contractile phenotype after this period. Through fracture of the internal elastic membrane, these cells migrate into the intima, where they may continue to proliferate and synthesize extra-cellular matrix, which will ultimately constitute the bulk of the restenotic lesion.

Recent experimental data have suggested that adventitial myofibroblasts (an α-actin staining cell) also proliferate and migrate into the neointima[42]. Therefore, the adventitia has been proposed to play an important role in supplying the intima layer with proliferative cellular elements for new lesion formation. The adventitia may further be implicated in vascular remodeling[33, 42-44], since myofibroblasts are capable of collagen synthesis and tissue contraction as seen in wound healing[45].

Last but not least, extra-cellular matrix (ECM), composed of various collagen sub-types and proteoglycans[46] actually constitutes the major component of the restenotic lesion; neointimal hyperplasia has been shown to be predominately a low cellular tissue[47]. Constituents of ECM, such as hyaluronan, fibronectin, osteopontim and vitornectin also facilitate SMCs migration[48-50]. In addition, reorganization of the ECM, replacing hydrated molecules by collagen, may result in retraction of vessel wall[51].

A New Paradigm of Restenosis: Vascular Remodeling

The ultimate clinical consequence of the above described puzzling processes is late lumen renarrowing. The relative contribution of each of the phenomena, vascular remodeling and neointimal hyperplasia, to the occurrence of restenosis may vary considerably from one patient to another and even from one site to another in a same vessel[52].

Elastic recoil has been characterized a decade ago by means of quantitative angiography[53] to occur immediately after balloon angioplasty[54, 55] as a consequence of the natural elastic property of blood vessels to respond to stretch. Thus, this phenomenon is of doubtful utility for the process of late lumen renarrowing.

Neointimal proliferation was originally described as the most important mechanism of restenosis based on extensive experimental and autopsy works as described above[56-58]. Based on this assumption, several clinical studies were conducted in attempts to prevent restenosis using pharmacological antiproliferative agents, but results have been largely disappointing[59-72]. We now know that only half of late lumen loss following PTCA procedures is due to intimal hyperplasia[59] and a new paradigm of restenosis has emerged: vascular remodeling[14, 63, 73-76].

The chronicle change of coronary artery dimensions was first described in 1972 by Mann et al[77], who observed that African Masai tribesmen maintained lumen dimensions despite substantial atherosclerosis. Later, Glagov et al[78] demonstrated that vessel enlargement compensates for atherosclerotic plaque increase, maintaining lumen dimensions. In this elegant autopsy work[78], up to 40% increase in plaque volume was neutralized by vessel enlargement; after reaching this threshold, lumen reduction was directly proportional to plaque growth. Subsequently, similar compensatory mechanisms have been proposed to explain the restenotic process[14, 74] and vessel shrinkage has been observed as an important determinant of late lumen reduction[75, 76].

Intravascular ultrasound (IVUS), due to its ability to image structures of the vessel wall [79, 80] in vivo, has played a central role in clarifying the relative contribution of new tissue growth and vessel constriction to restenosis. IVUS studies have provided clinical evidence that neointimal hyperplasia accounts to less than 50% of lumen reduction in non-stented coronary segments[81-84].

The term remodeling has been applied largely to describe either vascular shrinkage or

enlargement[85]. The definition proposed by Schwartz et al[85], in which remodeling is characterized in a continuous spectrum by any change in vascular dimension, may better describe this compensatory phenomenon. Quantitative angiographic studies showing that changes in lumen diameter after PTCA present a near-Gaussian distribution [86, 87] suggested that the response to PTCA is a generalized phenomenon rather than the previously held notion that restenosis was an "all or nothing" event. Subsequently, IVUS studies showing good correlation between changes in plaque and vessel cross-sectional areas have determined the compensatory aspect of the remodeling process after PTCA[81, 83, 84]. In this regard, our group carried out a detailed three-dimensional IVUS analysis of the local processes of restenosis. We observed, albeit preliminarily, that local changes in plaque volume correlated with changes in total vessel (external elastic membrane) volume, although both patterns of remodeling (enlargement and shrinkage) were found in individual balloon-injured coronary segments (unpublished data). Similarly, individual variability of the remodeling process has been reported by Pasterkamp et al in atherosclerotic femoral arteries[52].

The restenotic process was reputed by our group to be a device-specific phenomenon [88] which has been recently supported by IVUS studies [89]. Studies using volumetric IVUS analysis have further confirmed that remodeling is almost absent after stenting whereas it plays the major role in late lumen reduction after directional coronary atherectomy or balloon angioplasty[90-92].

Detection of Restenosis

Gruntzig et al. first observed that most clinical ischemic events related to vessel renarrowing occurred between 3 and 9 months after PTCA, mirroring the appearance of angiographic restenosis[93-95]. Considering that up to 30% of asymptomatic patients may exhibit angiographic restenosis (diameter stenosis > 50% at follow-up) [96] and that exercise electrocardiographic testing has limited value to detect "silent" restenotic lesions, other non-invasive tests such as thallium scintigraphy and stress echocardiography have been used to improve the sensitivity and specificity of non-invasive assessment of restenosis[97-99]. In clinical trials testing the effect of a given therapy on restenosis, objective angiographic criteria of restenosis have been preferred. When clinical outcome is also taken into account, repeat target vessel revascularization has been proposed as the most specific clinical restenosis end-point among other clinical markers (i.e., death, myocardial infarction, symptoms recurrence or combined major adverse cardiac events – MACE)[100]. Conversely, for clinical purposes, non-invasive assessment of recurrence of stenosis (symptomatic status and stress tests) in patients treated with PTCA appears an appropriate approach. This latter recommendation is based on a series of previous observations: 1) Routine angiographic follow-up may have increased, albeit small, morbidity and mortality[101]. 2) Asymptomatic patients with non-functional angiographic restenosis experience a benign course [102-104]. 3) The so-called occulostenotic reflex[105] leads to a higher rate of repeat revascularization with no clear clinical benefit at 12 months after the initial intervention[106]. 4) Late lesion regression at the dilated site may occur after both stenting and balloon angioplasty[107-109]. Undoubtedly, these data warrant a practical strategy of "watchful waiting" until recurrence of symptoms or non-invasive detection of ischemia occurs. If repeat angiography is carried out without clear clinical evidence of ischemia, sensor-tipped guide wires for measurements of distal flow velocity or pressure may be useful to assess functional status of restenotic lesions in the catheterization laboratory and assist physiologic-based decision making

regarding the need for reintervention[102, 110]. In fact, many clinical trials include the requirement for such testing at follow-up angio in patients with asymptomatic restenosis.

Coronary Angiography for Detection and Quantification of Restenosis

Angiographically detected lesions of 50% diameter stenosis or more at follow-up has been historically considered as representing "restenosis"[111]. This apparently arbitrary cutoff point was, in fact, founded on good scientific evidence, being based on physiological experimental studies which demonstrated that when the arterial lumen diameter is reduced to 50% or less, coronary flow reserve becomes impeded[112]. For purposes of scientific studies, many definitions of angiographic restenosis have been used[113]. The classical binary definition based on percentage diameter stenosis has not been universally accepted since it does not depict the concept of degree of deterioration in stenosis severity since angioplasty and does not convey a measure of the vessel response to injury[94, 100, 114]. The use of the term percentage diameter stenosis itself carries with it the assumption of normal-appearing reference segments, which is known from IVUS studies to be an erroneous assumption[79, 80, 115]. It seems unlikely that, in clinical practice, the pragmatic angiographic binary view of restenosis will be replaced by a less practical scientific perspective of a continuous phenomenon, although true progress in this area can only be made through the adoption of such scientific approach, particularly by the use of IVUS analysis[116]. In view of these considerations, clinical restenosis studies have been adopting a more comprehensive approach in reporting findings from both perspectives (categorical and continuous), to determine whether the agent under investigation had restraining or inhibitory effect and whether the ultimate clinical/angiographic outcome has been improved by the use of any new therapy. Quantitative coronary angiography (QCA) has been largely used to determine lesion severity and define restenosis in the clinical context [117-120], since visual assessment may lead to overestimation of the degree of narrowing in "severe" lesions and underestimation of the severity in "mild or moderate" lesions[121-123]. Furthermore, digital systems now permit on-line QCA in the catheterization laboratory, providing fast, easy and clinical relevant information for patient care[124]. Although, angiography has been widely used as the guiding tool for coronary disease management, the clinician should also consider functional, invasive or non-invasive, assessment of the restenotic lesion before referring the patient to additional coronary revascularization.

Is Restenosis Predictable?

Identification of factors associated with higher risk of restenosis may be useful in counseling patients whether to select a percutaneous intervention or other therapeutic strategies (clinical treatment or by-pass surgery). Unfortunately, there have been inconsistencies in linking restenosis to baseline demographic and clinical characteristics[125-128]. Diabetes mellitus and unstable angina have consistently been demonstrated to be important clinical risk-factors for restenosis[125, 126, 129-132]. Preliminary results from the Arterial Revascularization Therapy Study (ARTS) have further confirmed that diabetes mellitus is an important independent predictor of late clinical events in patients treated with multivessel PTCA[133]. Some anatomic characteristics have also been implicated with increase likelihood of restenosis; left anterior descending coronary artery, saphenous vein graft, small vessel diameter, lesion length and chronic total occlusion represent important anatomic characteristics that have been associated

with higher incidence of angiographic restenosis[126, 134-139]. Others have reported higher incidence of restenosis for lesions located proximally[140] and restenotic lesions[141, 142].
Although, prior knowledge of the subset of patients at higher risk of restenosis may be useful for clinical decision making, angiographic and IVUS studies have extensively demonstrated that the principal determinant of restenosis is the lumen size achieved at the end of the procedure[137, 143-149]. The amount of residual plaque burden has also been considered as an important predictor of restenosis [143, 150]. Conversely, the PICTURE study investigators[151] did not identify any IVUS parameter related to categorical angiographic restenosis. The use of long or multiple overlapping stents have also been associated with increased risk of restenosis[144, 152], whereas the influence of balloon inflation pressure and residual dissection on vessel renarrowing has yet to be clarified[153-155].
To help in predicting restenosis in the cath lab at the end of a procedure, our group has constructed simple reference charts, based on serial QCA and IVUS studies. These charts, derived from large cohorts of patients enrolled in prospective trials, provide useful information for patient care, considering that QCA and/or IVUS analysis may be performed online and that such parameters are partially operator dependent[137, 144]. Functional parameters derived both from post-procedure coronary flow velocity reserve (CFR) or fractional flow reserve (FFR) in combination with morphological (angiography) have been shown to predict restenosis after PTCA[156-158]. In the DEBATE study[157], distal CFR > 2.5 associated with angiographic residual stenosis <35% identified lesions with low restenosis rate (16% versus 41%). Similarly, another non-randomized study[158] has shown that patients with both FFR >0.9 and angiographic residual stenosis <35% had high event free-survival rate at 12 months (92% versus 69%). The combination of these parameters must be thus considered a relevant practical approach in interventional therapy and day to day practice.

Luminal Geometry and Restenosis:

The Importance of Interventional Effectiveness

The "bigger is better" philosophy[159], in which the lumen size obtained after PTCA will ultimately determine the occurrence of restenosis, has been largely accepted. One may question the beneficial effect of optimized intervention since neointimal response has been shown to be proportional to the magnitude of vessel injury [47, 160], in other words "the more you gain, the more you lose". Both concepts, apparently contradictory, are fundamentally correct, and the ultimate determinant of late lumen size will be the balance between acute gain and late loss. It is now clear that the "the bigger, the better" principle holds true for any interventional device, although the favorable relationship between late loss and acute gain appears to be a device-specific phenomenon[88]. Recent studies applying the concept of optimized intervention have reported lower restenosis rates as compared to their "old brothers" studies using similar devices [105, 157, 161-172]. Although IVUS is unequivocally useful to guide and confirm the achievement of an optimal lumen gain, particularly in stented segments, the risk of restenosis still remain clinically relevant[148]. In addition, the cost-effectiveness of IVUS guided optimized stent deployment has yet to be demonstrated. In the MUSIC study, applying a strict IVUS criteria of optimal stent deployment in a selected population, impressive long-term results were observed (binary restenosis rate of 8.3%)[165]. The CRUISE study investigators have also shown

favorable results after IVUS guided stenting: reduction of target lesion revascularization from 14.9% (IVUS documented group) to 8.9% (IVUS guided)[148]. On contrary, final results from the RESIST[173] and preliminary data from the AVID and OPTICUS trials have not confirmed the benefit of IVUS guided stenting on late outcome.

Provisional Stenting and Direct Stenting

The strategy of "stent-like" balloon angioplasty with a stand-by stent to be implanted whenever needed (so-called provisional stenting) has emerged from the impressive good long-term results observed in the cohort of patients treated by BA and with a post-procedure diameter stenosis < 30% in the BENESTENT trial[174]. Although others have not confirmed these results[175, 176], provisional stenting has become an attractive strategy[157, 158, 177-180], since it may represent reduction in costs and good long-term outcome when a "stent-like" result is obtained with balloon angioplasty alone. Additionally, the treatment and the long-term outcome of patients with in-stent restenosis remain a matter of concern[181-184].

Before unconditionally applying the strategy of provisional stenting in daily practice, one should consider that routine stent implantation was cost-effective in the BENESTENT II trial, and that the sub-group of patients with "stent-like" result after BA had a clinical outcome still 6% inferior to the stented patients[105, 164]. Reduction in both costs and restenosis rate may be further obtained by applying a strategy of direct stenting (without balloon pre-dilatation), although such benefit needs to be confirmed in randomized clinical trials[185, 186].

It is unlikely that stent-like results will be achieved by BA without adjunctive IVUS or physiological assessment, which may ultimately increase the cost of the procedure[153]. Indeed, preliminary data from the DEBATE II trial, in which optimal results were guided by QCA (residual diameter stenosis <35%) and Doppler Flow wire (CFR >2.5) measurements, showed that both primary (unconditional) and provisional stenting strategies had similar one-year clinical outcome and primary stenting was more cost-effective. Interesting and somewhat puzzling was that an improvement in event-free survival at one year was further achieved by stent implantation after an initial stent-like balloon angioplasty. In view of these considerations, a strategy of provisional stenting will not improve clinical outcome or reduce costs of PTCA procedures, but it may postpone stenting in up to 50% of the patients, which may have some benefit, considering the insidious and "malignant" problem of in-stent restenosis.

The role of "New" Intervention Devices in the Prevention of Restenosis

Over the past decade several new devices (stent, directional, rotational or extractional atherectomy devices, excimer laser angioplasty, cutting balloon, etc) and strategies have been developed to limit the occurrence of restenosis, but no therapy has consistently achieved a single digit incidence of restenosis.

Intracoronary stents have unequivocally been shown to result in superior acute and late outcome as compared to balloon angioplasty[105, 157, 161-164, 187-191]. Therefore, these metallic prosthesis are being used in >50% of all intervention procedures worldwide[179, 192]. It is nevertheless important to note that stents do not inhibit, but rather enhance, the proliferative vascular response and that this metallic prosthesis diminishes restenosis as compared to balloon angioplasty by achieving a larger residual lumen and preventing vessel shrinkage (elastic recoil and negative remodeling).

Debulking devices (DCA, TEC, rotablator, laser angioplasty) have been reported as conferring no superior long-term results as compared to conventional balloon angioplasty and somewhat less than stenting[168-171, 193-196]. Favorable results after directional atherectomy studies using a strategy of aggressive debulking guided by IVUS have been reported recently[166, 167]. But these were obtained by operators experienced with the technique of DCA and such a strategy is more costly, so that the use of DCA should be restricted to non-calcified lesions proximally located in the left descending anterior coronary or bifurcation lesions[153, 197, 198]. The SOLD registry[199] has suggested a potential benefit (11% angiographic restenosis) of aggressive plaque debulking followed by stent implantation in such selected lesions. The synergistic hypothesis of debulking prior to stenting[199-201], although not yet validated in large randomized trial, is supported by recent IVUS study from the same group of investigators involved in the SOLD registry showing that the amount of residual plaque outside the stent correlates with long-term outcome[150].

Preventive Therapies

Pharmacological Prevention of Restenosis

The focus of the prevention of restenosis over the past 2 decades has been through the application of pharmacological agents. Unfortunately, the great majority of clinical studies have not reproduced the promising results observed in the experimental laboratories[59-72].
Data from the EPIC study suggested a reduction in the need for second intervention in high-risk patients treated with monoclonal antibody against the platelet glycoprotein IIb/IIIa[202]. However this hypothesis was not confirmed in subsequent trials using either a similar medication (abciximab) or other antagonists of GP IIb/IIIa[69, 203]. A potential anti-restenotic effect of abciximab on diabetic patients has been observed in a sub-analysis of the EPISTENT study[204], but these results have yet to be validated[205].
A small number of studies on pharmacological intervention to prevent restenosis have shown satisfactory results[206-211]. Before sweeping changes in clinical practice these findings should be further confirmed.
Local drug delivery devices, including drug-coated stents, and even more sophisticated cell-based vascular gene-delivered systems have been developed[192, 212], however the clinical application and efficacy of such therapies remains to be demonstrated.

What about brachytherapy for prevention of restenosis?

A new therapy, intracoronary gamma-radiation, has been reported to significantly reduce re-restenosis after successful re-stenting of in-stent restenosis[213]. Preliminary data from prospective studies, using either beta (BETA WRIST) or gamma radiation (WRIST, GAMMA1), have recently confirmed the good results of catheter-based radiation therapy for the treatment of in-stent restenosis: 40-70% reduction in restenosis as compared with placebo.
Brachytherapy, either by means of catheter based-systems or radioactive stents, has also been used for prevention of restenosis in less "malignant" *de novo* coronary lesions [214-218]. However, the long-term safety of this novel therapeutic modality has been argued[219], and before incorporating intracoronary radiation in daily clinical practice some problems must be

solved: stent and/or radiation edge restenosis[216], late thrombotic occlusions[220] and potential delayed restenosis[221-224].

How to deal with restenosis if we failed to prevent it?

Restenotic lesions have been associated with an increased risk of re-restenosis as compared with "de novo" lesion. However, satisfactory results (18% restenosis rate) have been observed by treating restenosis after balloon with stent implantation[191].
Conversely, treatment of in-stent restenosis represents the new challenge for the interventional cardiologist[153, 182]. Treatment of diffuse in-stent restenosis has been associated with high (45-80%) rates of target lesion revascularization, regardless of the device used (balloon angioplasty, stent, rotational atherectomy or laser angioplasty)[181, 183, 184, 225, 226]. As discussed above, intracoronary radiation, is the sole therapeutic approach that has proved clinically its efficacy for the treatment of in-stent restenosis.

Future Directions

Researchers are still seeking solutions for restenosis, but the cure has not yet been found. Taking advantages of the accumulated knowledge in the past 2 decades, many innovative approaches have been developed. Biodegradable stents, which "dissolves" 9 months after implantation, have recently been implanted in humans with promising results[227]. Sophisticated energy-based therapeutic modalities (phothodynamic therapy, sonotherapy, cryotherapy) have also emerged as potential solutions and clinical studies are already underway.
Undoubtedly we have come a long way in the last decade. More patients with complex coronary disease are being treated percutaneously using innovative strategies, many as an out patient basis. PTCA is safer acutely than ever and bypass surgery is progressively being reserved for patients when percutaneous techniques appear impossible or inappropriate.
The frequency of significant clinical recurrence of treated lesions is certainly less than 20 years ago but still represents the Achilles heel of the percutaneous approach. We have not founded the "magic bullet" or the "Holy Grail" and maybe we never will since the search seems to reveal more and more the complexity and multifunctional nature of the pathological process leading to the blockage we see in the angiogram. Nevertheless we and our patients take heart from the progress already made and the commitment shown to find a solution for restenosis.

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CHAPTER 2

Indirect Evidence for a Role of a Subpopulation of Activated Neutrophils in the Remodeling Process after Percutaneous Coronary Intervention

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Abstract

Aim: Leukocytes have been implicated in the restenosis process after percutaneous transluminal coronary angioplasty. We investigate the association of the activated status of circulating neutrophils and restenosis after angioplasty.

Methods and results: The population consists of 108 patients treated for single, de novo lesions located in native coronary arteries with elective balloon angioplasty (n=44) or stenting (n=64). Pre-, post-procedure and at 6-month follow-up angiograms were analyzed by an independent core lab. Blood sample was collected immediately before treatment and the antigen CD66, which is specifically expressed by activated neutrophils, was measured. Overall, the average expression of CD66 was 6.4±3.6 mean fluorescence intensity. In the stepwise linear regression model, which included biological, clinical and angiographic variables, absolute gain showed a direct association ($p<0.001$) with relative late loss (Relative late loss = absolute late loss ÷ pre-procedure reference diameter), whereas CD66 expression was inversely associated with relative late loss ($p=0.004$). CD66 expression also showed an inverse association with relative late loss in the balloon angioplasty treated patients ($p=0.002$, $\beta=-0.49$). In the stent subgroup, only reference vessel diameter and acute gain were independent predictors of relative late loss.

Conclusion: Our results confirm the beneficial role of pre-procedure activated status of neutrophils in the restenotic process after balloon angioplasty. The lack of relationship between CD66 expression by neutrophils and relative late loss after stenting suggests that this leukocyte may be involved in the remodeling process.

Introduction

The technique of percutaneous transluminal coronary angioplasty has undergone tremendous improvement. However, the recurrence of coronary stenosis is still a major problem in interventional cardiology. Some years ago, it became clear that differences in vascular remodeling play a major role in the restenotic process after balloon angioplasty[1-4].

The understanding of the biochemical mechanism of the restenotic process is of clinical relevance, since specific therapies could be developed to reduce the unsolved issue of restenosis after percutaneous coronary interventions. Therefore, the contribution of leukocytes to the restenotic process has been investigated[5-8]. Recently, it has been suggested that granulocytes do not contribute to the occurrence of intimal hyperplasia[9] confirming the findings of Rogers et al. about the central role of monocytes in that process[10]

Further, we have found that pre-procedure expression of the CD66 receptor by neutrophils is associated with a better angiographic prognosis after balloon angioplasty[5]. While many activation markers were studied, the activation status of the neutrophil relevant for the angiographic outcome was best characterized by the magnitude of CD66 expression[5]. Although inflammation leading to weaker adventitial layers has been suggested to induce positive remodeling in experimental model[11, 12], the exactly mechanism (neointimal formation or remodeling) involved in the potential beneficial effect of neutrophils on restenosis is still unknown.

The neutrophil CD66 antigen, differently from the CD11b/CD18 receptor, is exclusively expressed by granulocytes and is considered to be an activation marker as well[13]. The CD66 family members expressed by granulocytes have been found to be associated intracellularly with tyrosine kinases like Lyn and Hck that mediate signal transduction from the receptor[14]. It is not known if CD66 could serve as a marker for a subpopulation of neutrophils that play a specific role in the mechanism of restenosis. Neutrophils express four different CD66 members belonging to a group of highly glycosylated proteins of the carcinoembryonic antigen family,

i.e., CD66a, Cd66b (formerly known as CD67), CD66c, and CD66d[15]. CD66a and CD66b are stored in the secondary granules, while CD66c is present in the primary granules of the neutrophil[16-18]. Upon ligation, these molecules may regulate CD11b/CD18-mediated adhesion without the functional activation of that receptor and potentiate the production of reactive oxygen species[19-21]. To our knowledge, the variation in CD66 expression in humans has not yet been extensively studied.

The aims of the present study were first to validate the unexpected finding of our pilot study[5] concerning the inverse association between relative late lumen loss and the pre-procedural expression of the neutrophil activation marker CD66, and finally to discriminate in which of the two components of restenosis (neointimal hyperplasia and/or remodeling) activated neutrophils expressing the specific receptor CD66 may contribute. Thus, we determined the association of the expression of CD66 before the procedure and late luminal renarrowing in an independent group of balloon angioplasty patients, and in a population treated with stent implantation.

Methods

This study consists of a cohort of 108 consecutive patients successfully treated with elective balloon angioplasty (n = 44) or stent implantation (n = 64) at the Thoraxcenter. All patients were treated for single-vessel, short (< 20 mm) and de novo lesions located in native coronary arteries. Patients treated during the acute phase of myocardial infarction as well as those with in-hospital complications after the procedure (myocardial infarction, repeat revascularization or subacute thrombotic occlusion) were excluded. The protocol was approved by the Medical Ethical Committee of the Erasmus University Hospital, Rotterdam and all patients provided written inform consent.

Protocol

Sheaths (7 or 8 French) were inserted into the arterial and venous femoral vessels. Thirty milliliters of blood was collected from the venous sheath immediately before treatment, anticoagulated with 0.2% EDTA, and kept at 4°C. The method of revascularization, balloon angioplasty or stenting was based on operator's preference as well as the type of stent to be implanted. The devices (balloon or stent) were sized according to the reference vessel diameter and lesion length. The procedures were performed according to standard clinical practice, with high-pressure (at least 12 atmospheres) post-stenting balloon inflation. All patients received aspirin (250 mg/day) at least 24h before the procedure, whereas stented patients also received ticlopidine (250mg twice a day, maintained for a period of 30 days after the procedure).

Quantitative Coronary Angiography

Coronary angiograms were obtained in each patient pre-, post-procedure and at 6-month follow-up. All angiograms were analyzed using the CAAS system (Pie Medical BV, Maastricht, The Netherlands) according to previously described methodology[22]. Measurements were performed in multiple (≥ 2) matched angiographic views after intracoronary nitrates were administered. The contrast-free guiding catheter was selected for calibration and interpolated reference vessel diameter at the computer-defined minimal lumen site was automatically calculated. All measurements were performed off-line by an independent Core Lab (Cardialysis BV, Rotterdam, The Netherlands) which was unaware of the biochemical analysis results.

Continuous angiographic criteria of lumen change has been largely used in clinical trials and more closely reflect the magnitude of the reactive intimal hyperplasia, compared to dichotomous

variables such as > 50% diameter stenosis[23, 24]. Thus, in accordance to our pilot study, we choose relative late loss as the dependent variable. Relative late loss was calculated as absolute late loss (minimal lumen diameter post – minimal lumen diameter at follow-up) divided by pre-procedure reference diameter. In taking the reference vessel size into account, this parameter may better address the impact of vascular lumen reduction compared to absolute late loss. For comparison, we used other angiographic variables loss index (absolute late loss divided by minimal lumen diameter post) and net gain (minimal lumen diameter at follow up – pre-procedure minimal lumen diameter) as well.

Reagents

The monoclonal antibody (mAb) used in the flow cytometric analysis of membrane antigen expression was mAb CLB-gran10 directed against CD66acde (the Central Laboratory for Blood transfusion, Amsterdam, The Netherlands).

Flow Cytometric Analysis of membrane Antigens

To prevent any staining-procedure-related activation the leukocytes were kept on ice during the entire procedure to inhibit their normal metabolic processes. Furthermore, the reagents were endotoxin free. Erythrocytes in the blood sample were lysed with a sterile ammonium chloride solution consisting of 155 mM NH_4Cl, 10 mM $NaHCO_3$ and 0.1 mM EDTA at 4°C. This procedure does not alter the expression of CD66(b) and of various other membrane activation markers of the neutrophil[25]. Next, the leukocytes were washed two times with sterile, ice-cold phosphate-buffered saline (PBS; in mM: 140 NaCl, 1.5 KH_2PO_4, 8.1 $Na_2HPO_4.2H_2O$ and 2.7 KCl; pH 7.4), and finally resuspended at a concentration of 2 x 10^7 cells/ml sterile PBS modified according to Becton Dickinson (PBS^{BD}; in mM: 43 K_2HPO_4, 10 $NaH_2PO_4.H_2O$, 123 NaCl, and 0.02% NaN_3 and 0.5% bovine serum albumin; pH 7.2) at 4°C. Next, 5 x 10^5 leukocytes were incubated with the mAbs or mouse IgG_1 (negative control) for 30 min at 4°C, washed two times with ice-cold PBS^{BD} and then incubated with fluorescein isothiocyanate (FITC) conjugated rabbit $F(ab')_2$ anti-mouse IgG_1 (STAR9; Serotec) for 30 min at 4°C in the dark. The cells were washed two times and fixed with 1% paraformaldehyde in PBS^{BD}. The duration of this procedure from the time of collection until fixation amounted to 3-4 hr. Until the cells could be analyzed (< 1 wk), they were stored at 4°C in the dark. The binding of mAb to the cell surface was quantified by fluorescence-activated cell sorting (FACStar, Becton Dickinson, Etten-Leur, The Netherlands). Five thousand events were acquired after live gating of the neutrophils with the use of forward versus sideward scatter. Antigen expression is presented as specific median fluorescence intensity.

Statistical Analysis

Variation in duplicate measurements (intra-assay variation) did not exceed 10%. Univariate linear regression analysis was performed to determine the association between relative late loss after treatment and each biological, clinical, angiographic, and procedure- related variables. In order to establish the independent risk factors, each variable that proved to be statistically significant ($p<0.05$) were entered in a stepwise multivariate linear regression model with "*p*" values for inclusion and elimination set at 0.05 and 0.10. We also performed separate analyses for each different therapeutic population, balloon angioplasty and stent. The correlation between

pre-procedure variables (clinical, angiographic) and the level of CD66 expression by neutrophils was also tested using univariate linear regression.

Results

Baseline characteristics are shown in table 1. Pre-, post- and follow-up angiographic results are summarized in table 2. The expression of the neutrophil membrane receptor CD66 ranged from 0 to 22.42 mean fluorescence intensity (average value of 6.4 ± 3.6). No relationship between the biological markers and clinical (including unstable angina, Braunwald classification class I-IIIA) or angiographic pre-procedure variables was found in our study. The mean CD66 expression was 5.5 ± 2.1 mean fluorescence intensity in the stent group and 7.6 ± 4.7 mean fluorescence intensity in the balloon angioplasty group.

Table 1. Baseline clinical characteristics

Variables	Total (n=108)	Balloon Angioplasty (n=44)	Stent (n=64)
Age, years	57 ± 9.3	55 ± 8.3	59 ± 9.6
Gender, male, %	51	38	60
Diabetes, %	5	11	0
Hypercholesterolemia, %	14	11	15
Smoking, %	33	31	33
Hypertension, %	39	40	39
Previous myocardial infarction, %	18	3	28
Previous bypass surgery, %	7	0	12
Unstable angina, %	27	22	29
Left anterior descending artery , %	43	45	40

Predictors of relative late loss in the total population (n = 108)

We identified several univariate predictors of relative late loss: expression of CD66, the use of stent, minimal lumen diameter post, and absolute gain (table 3). No clinical variable was correlated with relative late loss. By stepwise linear regression, only absolute gain and CD66 remained as independent predictors of relative late loss (table 3). Absolute gain showed a direct correlation with increase relative late loss, whereas the expression of CD66 showed an inverse association with relative late loss.

Predictors of relative late loss after balloon angioplasty

In a separate analysis, we found some univariate predictors of relative late loss in the population treated with balloon angioplasty (n = 44): expression of CD66, target site in the LAD and diabetes (table 3). In the multivariate regression model, target site located in the LAD and the expression of CD66 remained as independent predictors of relative late loss. Treatment of LAD was directly related with relative late loss after balloon angioplasty, whereas the expression of CD66 remained inversely associated with relative late loss. The pre-procedure expression of CD66 was also statistically significant inversely related to the conventional variables absolute late loss and loss index, but directly related to net gain (not shown).

Table 2. Off-line Quantitative Coronary Analysis

Parameters	Total (n=108)	Balloon angioplasty (n=44)	Stent (n=64)
Pre-procedure			
Reference Diameter, mm	2.84 ± 0.5	2.76±0.5	2.89±0.6
Minimal Lumen Diameter, mm	0.99 ± 0.44	0.99±0.41	0.99±0.46
Diameter Stenosis, %	65.7 ± 13.3	64.5±12.5	66.6±13.9
Post-procedure			
Reference Diameter, mm	3.1 ± 0.57	2.85±0.6	3.2±0.5
Minimal Lumen Diameter, mm	2.36 ± 0.61	1.97±0.52	2.6±0.52
Diameter Stenosis, %	23.6 ± 11.2	33±7	18±8
Acute gain, mm	1.32 ± 0.63	0.97±0.5	1.6±0.6
Follow-up			
Reference Diameter, mm	2.83 ± 0.58	2.78±0.54	2.85±0.59
Minimal Lumen Diameter, mm	1.7 ± 0.68	1.6±0.6	1.7±0.7
Diameter Stenosis, %	42.1 ± 20.1	42.5±15	41.9±22
Late Loss, mm	0.66 ± 0.73	0.28±0.53	0.9±0.74
Relative Late Loss	0.22 ± 0.26	0.1±0.2	0.3±0.25

Predictors of relative late loss after stenting

No biological risk factor was associated with relative late loss in the stent population (n = 64). Scatterplots showing the association of the expression of the membrane antigen CD66 and relative late loss in the balloon angioplasty and stented patients are illustrated in figure. Two angiographic variables were independent predictors of relative late loss: pre-procedure reference vessel diameter and acute gain (table 3).

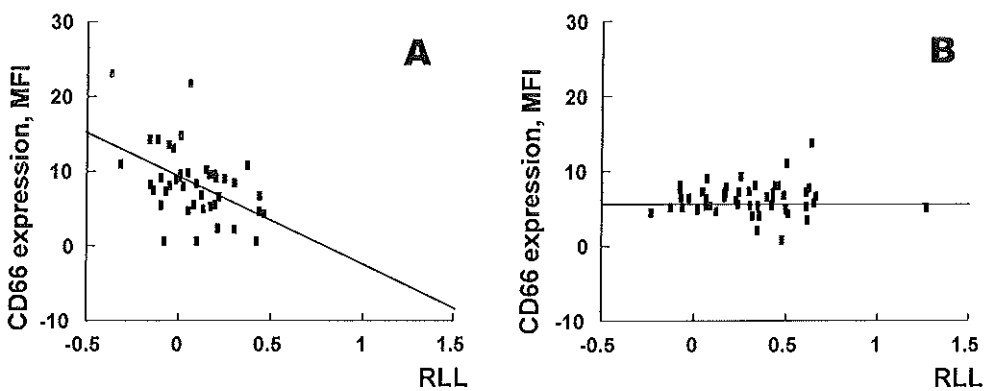

Figure 1.
Scatterplots showing the association between the expression of CD66 antigen by neutrophils and relative late loss (RLL) after 6 months according to the population investigated: **A** – in balloon angioplasty patients this association can be described by the equation: $y = 8.97 - 11.67x$ (n=44; p=0.001, R^2=0.232) and **B** – in stented patients this association can be described by the equation: $y = 5.58 + 0.17x$ (n=64; p=0.9, R^2=0.000).

Table 3. Predictors of Relative Late Loss after percutaneous intervention

Variable	Total (n = 108)				BA (n = 44)				Stent (n = 64)			
	Univariate	Multivariate			Univariate	Multivariate			Univariate	Multivariate		
Clinical	p	p	b	ß	P	p	b	ß	p	p	b	ß
Age	NS				NS				NS			
Sex, male	0.08				NS				NS			
Diabetes	NS				0.051	NS			NS			
Unstable angina	NS				NS				NS			
Previous MI	NS				NS				NS			
Previous angioplasty	NS				NS				NS			
Left anterior descending	NS				0.002	0.002	0.2	0.49	NS			
Angiographic												
Pre reference diameter	NS				NS				0.06	0.01	-0.17	-0.38
Pre minimal lumen diameter	NS				NS				NS			
Procedure-related												
Post reference diameter	NS				NS				NS			
Post minimal lumen diameter	< 0.001	NS			0.07	NS			NS			
Absolute gain	< 0.0001	< 0.0001	0.159	0.375	NS				0.03	0.03	0.16	0.32
Stent	< 0.0001	NS										
Biological markers												
CD66	0.002	0.004	-2.18	-0.278	0.001	0.002	-2.19	-0.49	NS			

pre = pre-procedure, post = post-procedure.
CD66 means the expression of this antigen by circulating neutrophils before the procedure.

Discussion

The present investigation corroborates the results of the pilot study[5] showing that activation status of circulating neutrophils, as demonstrated by the expression of the CD66 antigen, is inversely related with late coronary lumen loss after percutaneous coronary intervention. The standardized regression coefficients (β) of CD66 were similar in both the present study (balloon angioplasty group) and the pilot investigation[5] (-0.49 and –0.47, respectively). However, the expression of this antigen did not show any relationship with vessel renarrowing after stenting.

This could be relevant for the understanding of the role of neutrophils in preventing luminal renarrowing after angioplasty, since stent almost abolishes the contribution of remodeling to the restenotic process and has been considered as a pure model to investigate neointimal hyperplasia[26, 27]. Thus, the finding that activated neutrophils expressing the CD66 antigen may prevent vessel renarrowing after balloon angioplasty, but not after stenting, may encourage us to speculate that circulating phagocytes play a role in the mechanism of vessel remodeling after injury. Indeed, inflammatory mediators have already been shown to promote vessel enlargement in experimental model[11, 12]. However, limitations of angiography to directly assess vascular remodeling after angioplasty should be taken into account before drawing any definitive conclusion. Further, the study population was not randomly divided to be treated with plain balloon angioplasty or stenting, which may have introduced an unwanted source of bias.

In the process of geometric remodeling of the vessel upon vascular injury alterations in extracellular matrix metabolism, specifically collagen redistribution, appears to be an important factor[28]. In restenotic lesions total collagen content and collagen organization are significantly less in comparison with nonrestenotic vessels. While smooth muscle cells and fibroblasts produce various matrix proteins upon stimulation by cytokines secreted by monocytes in the lesion, these proteins on their turn could be degraded by matrix metalloproteinases. Neutrophils can release a soluble factor that activates endothelial cell matrix metalloproteinase-2[29]. On this basis, a negative role of neutrophils in the remodeling process would be expected. On the other hand, while the exact function of CD66 is currently unknown, it is noteworthy that gonococci expressing distinct opacity outer membrane proteins enter granulocytes via this receptor without stimulating their bactericidal repertoire using the phagocytes as an intracellular niche to survive[31]. Can this particular subpopulation of neutrophils prevent the change in phenotype of the myofibroblasts and smooth muscle cells, or the activation of the metalloproteinase cascade? Presently, no adequate mechanistic answer can be given. However, if CD66-expressing neutrophils accumulate at the site of injury and this receptor is stimulated properly, its distinct signaling pathway[30] may lead to the beneficial action as indicated by this study. Clearly, the underlying mechanism of the beneficial effect of CD66-expressing neutrophils on late lumen renarrowing after balloon angioplasty requires further investigation.

Monocytes appear to be an important contributing factor to neointimal formation after vascular injury. Accordingly, the administration of antibodies to the CD11b or CD18 receptor subunits was shown to prevent intimal hyperplasia upon angioplasty or stent implantation in experimental animal models[10, 32]. However, granulocytes also express the CD11b/CD18 or Mac-1 adhesion receptor and are recruited early to the traumatized vascular wall[33-37]. Thus any intervention directed to the Mac-1 receptor would prevent the entry of both monocytes and granulocytes into the lesion site, in fact revealing the net effect of the separate actions of each individual cell type. In a number of experimental models of vascular injury, in which neutrophils predominated in the lesion, the administration of monoclonal CD18 antibodies have failed to inhibit neointimal formation[9, 38, 39]. This indicates that neutrophils may not be involved in this process. However, prevention of the local accumulation of neutrophils by using of antibodies blocking the granulocyte-specific CD66 receptor should demonstrate that the action

of granulocytes does not contribute to, or even may compensate, the stimulatory effect of monocytes on intimal hyperplasia.

Other well-known angiographic risk factors, such as target lesion located at the left anterior descending coronary artery in the balloon population and reference vessel diameter and acute lumen gain in the stent group, were retained in the multivariate model. Left anterior descending artery has been associated with higher restenosis rate after angioplasty[40]. Greater acute gain has already been shown to stimulate proliferative response[40], which may reflect the higher degree of vessel wall injury in this situation[40, 41]. Finally, reference diameter was inversely associated with late lumen renarrowing, which may highlight the importance of vessel size in the outcome of patients treated with stents[42]. However, it should be considered that, by definition, vessel size is inversely correlated with relative lumen loss (relative lumen loss = late loss divided by reference diameter). No correlation between CD66 expression and unstable angina was observed, however it should be considered that all treatments were carried out in an elective basis. Thus, most of the patients were actually stable at the time of the procedure when the blood samples were collected.

Taken together, this study confirms that pre-procedure activation status of circulating neutrophils expressing the CD66 antigen exerts a protective influence on late vessel renarrowing after percutaneous coronary intervention and further suggests that these leukocytes may be implicated in the mechanism of vascular remodeling.

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CHAPTER 3

Three-Dimensional Intravascular Ultrasonic Assessment of the Local Mechanism of Restenosis After Balloon Angioplasty

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Abstract

Objective: To assess the mechanism of restenosis after balloon angioplasty. **Design:** Prospective study. **Patients:** 13 Patients treated with balloon angioplasty. **Interventions:** 111 coronary sub-segments (2-mm each) were analyzed after balloon angioplasty and at 6-month follow-up using 3-dimensional IVUS. **Main outcome measures:** Qualitative and quantitative IVUS analysis. Total vessel (external elastic membrane), plaque, lumen volume were measured in each 2-mm sub-segments. Delta values were calculated (follow-up – post-procedure). Remodeling was defined as any (positive or negative) changes in total vessel volume. Results Positive remodeling was observed in 52 sub-segments, whereas negative remodeling occurred in 44. Remodeling, plaque type and dissection were heterogeneously distributed along the coronary segments. Plaque composition was not associated with changes in IVUS parameters, whereas dissected sub-segments had greater increase in total vessel volume than those without dissection (1.7 mm^3versus -0.33 mm^3, p=0.04). Change in total vessel volume was correlated with changes in lumen ($p<0.05$, r=0.56) and plaque volumes ($p<0.05$, r=0.64). The site with maximal lumen loss was not the same site as the minimal lumen area at follow-up in the majority (n=10) of the vessels. In the multivariate model, residual plaque burden had an influence on negative remodeling (p = 0.001, 95%CI: -0.391 to -0.108), whereas dissection had an effect on total vessel increase (p=0.002, 95%CI: 1.168 to 4.969). **Conclusions:** Restenosis after balloon angioplasty appears to be determined by unfavorable remodeling. However, different patterns of remodeling may occur in individual injured coronary segment, which highlight the complexity and influence of local factors in the restenotic process.

Recurrence of stenosis is still an important drawback of percutaneous coronary interventions. The restenotic process is multi-factorial and several elements have already been identified: thrombosis, inflammation, smooth muscle cell proliferation and elaboration/degradation of extra-cellular matrix.[1][2] The clinical consequences of these processes are acute recoil, neointimal hyperplasia and vascular remodeling as determined by angiography and intravascular ultrasound.

The classical binary definition of restenosis is based on coronary angiography (> 50% diameter stenosis). Although clinical decision-making is in essence a "binary" process, the restenotic phenomenon cannot be comprehensively analyzed by luminographic methods.[3] In this regard, intravascular ultrasound (IVUS) has become an essential tool due to its ability to image structures of the vessel wall.[4] Furthermore IVUS assessed vessel wall remodeling has been proposed as an important factor in the recurrence of stenosis after balloon angioplasty.[5][6]

The issue of restenosis has been scrutinized over the last years, but some questions persist. The relative contribution of remodeling and plaque growth to the restenotic process is still debatable.[5][6][7][8][9][10][11][12][13] To assess the mechanism of restenosis, previous studies selected the cross-section with the narrowest lumen area pre-procedure[5], follow-up[6] or both.[7] Although these specific sites have unquestionable validity in the clinical context, they may not represent the location of maximal arterial wall response to injury (maximal lumen loss). Further, whether the pattern of arterial wall response to injury is homogeneously distributed along the entire target segment has yet to be investigated.

Three-dimensional intravascular ultrasound imaging with volumetric quantification allows us to address these issues.[14] Therefore, the present study incorporates this new technology to assess the mechanism of restenosis after balloon angioplasty.

Methods

PATIENTS

During 1997 and 1998, patients with de novo lesions in native coronary arteries, treated successfully with conventional balloon angioplasty, enrolled in prospective clinical studies were eligible for the present investigation. Only patients with scheduled 6-month follow-up and complete serial three-dimensional IVUS acquisition were included. Patients treated with any other percutaneous device (i.e., cutting balloon, direct coronary atherectomy, rotational atherectomy, laser ablation, stents, or radiotherapy) or those taking any specific medication under investigation were excluded. Angiographic inclusion criteria applied in the original studies consist of a reference vessel diameter > 2.5 mm and < 4.0 mm and a lesion length < 20mm.

Patients received aspirin (250 mg/day) and heparin IV (10.000 IU) before the procedure. Heparin was given to maintain the activated clotting time >300 sec. Aspirin was maintained after the procedure in all patients. Balloon angioplasty was performed according to standard clinical practice, and the selection of the balloon was left to the operators preference. In this cohort, the mean balloon artery ratio was 1.1. Post-procedure (after optimizing the results of balloon angioplasty) and follow-up IVUS imaging were acquired using the same motorized pullback system and after intracoronary nitrate infusion. The Medical Ethics Committee of University Hospital Rotterdam approved the protocol. All patients gave written informed consent.

THREE-DIMENSIONAL IVUS ASSESSMENT

Coronary segments were imaged with a mechanical IVUS system (CVIS, Boston Scientific Corporation, Maple Grove, MN) with a sheath-based IVUS 30 MHz catheter. ECG-gating image acquisition and digitalization 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] In the case of image acquisition using the motorized pullback without ECG triggering, the complete IVUS run was recorded in s-VHS tape for off-line three-dimensional reconstruction.[16]

A Microsoft Windows™-based contour detection program, developed at the Thoraxcenter, was used for off-line volumetric quantification.[17] Briefly, this program constructed longitudinal sections from the data set and identified the contours corresponding to the lumen and media boundaries. Checking and editing of the contours of the planar images were performed by two experienced analysts (MAC, KK). Intra-observer variability assessed by analyzing IVUS volumetric studies at least 3 months apart has been reported:-0.4 ± 1.1% and -0.65 ± 2.66% in lumen volume, -0.4 ± 0.6% and -0.19 ± 0.67% in EEM volume, -0.3 ± 1.0% and -0.95 ± 2.81% in plaque volumes using motorized pullback with and without ECG-gated, respectively.[15][16]

Three-dimensional IVUS image reconstruction and quantification has been validated previously.[15][16] This IVUS technology may confer some advantages over conventional IVUS assessment: 1) Visualization and quantification of the entire coronary segment (not only a single cross-section) allowing longitudinal assessment of the restenotic process.[6] 2) In a coronary segment of 20mm length, 100 cross-section areas may be measured which permit accurate identification of the sites with minimal or maximal lumen, plaque and/or EEM areas. Since the computerized contour-detection software automatically identifies these locations, comparisons between serial IVUS images can be performed in an "unbiased fashion", after both post-procedure and follow-up measurements have been completed. 3) Besides the use of

motorized continuous pullback (with or without ECG triggering)[18], precise location and matching of each cross-section can be further assured by comparing the multiple longitudinal views displayed by the three-dimensional reconstruction (figure 1). 4) After matched comparisons, the site with the maximal lumen loss may be readily identified, which may be essential for a mechanistic interpretation of the restenotic process.

The methodology to define the segment of interest has been previously described.[19][20] By the use of the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands), each angiographic sequence showing all balloon inflations may be displayed simultaneously on the screen and the location of the injured segment and its relationship with anatomical landmarks (aorto-ostial junction and/or side-branches) can be determined. Thus, the target segment injured by balloon inflation (20 mm long segment) was defined. These coronary segments were divided in 2 mm long sub-segments (each of them presenting 10 IVUS cross-sections) as described previously.[21] In this manner, the local pattern of the arterial response to injury can be investigated.

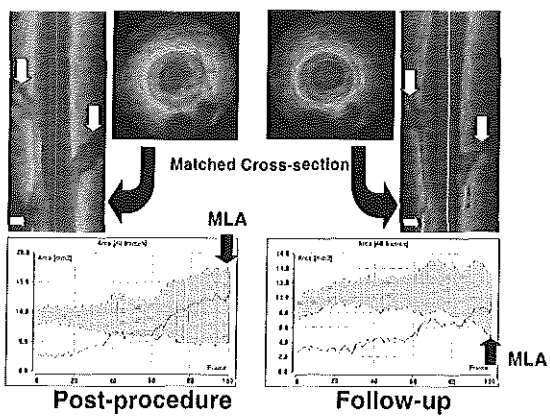

Figure 1. Standard display of the results by 3-D longitudinal reconstruction of the IVUS cross-sectional images using an ECG-gated pullback. **Upper outside panels:** Longitudinal reconstruction images at post-procedure (left side) and follow-up (right side) White arrows indicate the anatomical landmarks (sidebranches and calcium). **Upper inside panels:** Matched cross-sections immediately after the procedure (left side) and at follow-up (right side). **Lower panels:** Charts display the subsequent volumetric quantification at post-procedure (left side) and follow-up (right side).
The area values of the lumen (lower line) and total vessel (upper line) form the boundaries of the gray zone, which represent the plaque-media complex, and a single line depicts the absolute area value of plaque-media complex. Black arrows indicate the site of the minimal lumen area at follow-up (MLA).

QUALITATIVE ANALYSIS

All individual cross-sections were analyzed qualitatively by 2 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.[22][23] ADDINEach sub-segment 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 sub-segments were of the same type, as described previously.[21] In those cross-sections containing up to a 90° calcium arc, 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. Those sub-segments 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. The presence of dissection, defined as a tear parallel to the vessel wall[22], was also noted in each sub-segment.

QUANTITATIVE MEASUREMENTS AND DIFINITIONS

Total vessel volume determined by external elastic membrane boundaries and lumen volume were measured. Plaque volume was automatically calculated by subtracting lumen volume from total vessel volume. Delta values for each measurement were calculated (delta (Δ) = follow-up – post-procedure). Relative (percent) changes of IVUS parameters (delta volume / post-procedure volume) were also calculated in order to correct for differences in vessel size.

The location of the cross-section with the narrowest lumen area at follow-up was automatically reported. Retrospectively (after all measurements were performed), the sub-segment encompassing this specific cross-section (minimal lumen area site) was identified and the matched sub-segment of the post-procedure analysis was selected for comparison. Furthermore, the site with the maximal lumen loss was defined after the calculation of the delta values.

Remodeling was defined as a continuous process involving any (positive or negative) changes in EEM volume as proposed previously.[24] In the present study, enlargement or shrinkage of the vessel wall was considered when total vessel volume increased or decreased, respectively, compared to post-procedure measurement by at least two standard deviations (± 1.3%) of the intra-observer variability for repeat total vessel volume measurements.[15][16] In this manner, the potential intrinsic error of the method may be avoided.[25][26]

STATISTICAL ANALYSIS

Quantitative data are presented as mean ± standard deviation, whereas qualitative data are presented as frequencies. Continuous variables were compared by the use of unpaired Student's t test. Categorical variables were compared by means of Fisher's exact test. Linear regression (Pearson's regression coefficient) was performed to assess the correlation between changes in IVUS parameters. Multivariable linear regression models were built to identify predictors of changes in plaque volume and total vessel volume among qualitative and quantitative post-procedure IVUS parameters. A value of $p<0.05$ was considered statistically significant.

Results

In thirteen coronary segments injured by balloon inflation, 111 sub-segments were analyzed using three-dimensional IVUS volumetric quantification. Baseline characteristics of the patients are shown in Table 1. Nineteen sub-segments were excluded from the final analysis due to either diffuse calcified plaque (n=10) which precluded the quantification of the total vessel volume or side branches which involved >90° of the circumferential arc in more than 50% of the cross-sections (n=9).

QUALITATIVE ANALYSIS

Table 2 illustrates the variability of both type of plaque and presence of dissection distribution along the entire target segments. Only 3 patients had the same type of plaque distributed through the analyzed segment, whereas the presence of dissection detected in at least one injured sub-segment was noted in 9 patients.

Forty sub-segments (36%) were defined as soft, 53 (48%) as hard and 18 (16%) as normal/intimal thickening. Plaque composition was not related to changes in quantitative IVUS volumetric parameters. Sub-segments with hard plaques showed greater incidence of dissection compared with those with soft plaques (49% versus 23.7%, $p < 0.001$).

Overall, dissection was observed in 35 sub-segments (31.5%). Sub-segments with dissection had greater increase in total vessel volume as compared to those without dissection (1.7 mm^3versus -0.33 mm^3, p=0.04).

Table 1. Baseline and demographic characteristics.

Variables	
Age (years)	62.1 ± 5.96
Gender, male	13 (100%)
Diabetes mellitus	2 (15%)
Smoking	4 (29%)
Hypercholesterolemia	7 (54%)
Hypertension	4 (31%)
Previous MI	5 (39%)
Angina Status, CCS 3/4	10 (77%)
Treatment Site:	
Left Anterior Descending	5 (48%)
Circumflex Artery	4 (31%)
Right Coronary Artery	4 (31%)

MI means myocardial infarction, CCS means Canadian Class Society.

QUANTITATIVE ANALYSIS

Table 3 shows the mean values of changes (deltas) in IVUS parameters for all sub-segments of the entire target vessel, at the minimal lumen area location and at the maximal lumen loss site. The correlation between remodeling, changes in plaque volume and late lumen loss are shown in figure 2.

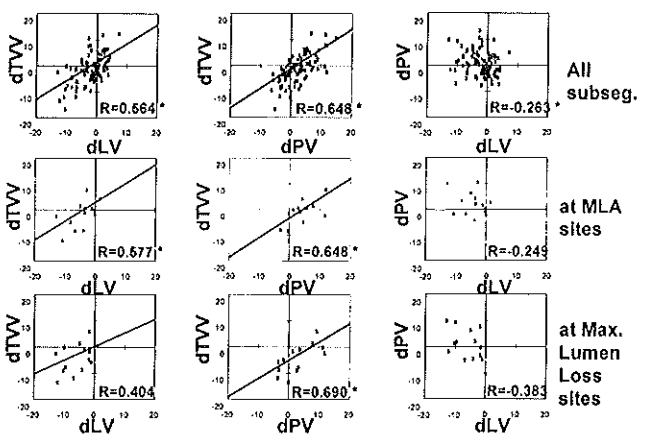

Figure 2. Correlation between remodeling (dTVV), changes in plaque volume (dPV) and changes in lumen volume (dLV).
Upper panels: Correlations in all sub-segments (n=111). **Middle panels**: Correlations at the sub-segments of minimal lumen area at follow-up (n=13). **Lower panels**: Correlations at the maximal late lumen loss sites (n=13). * = significant correlation ($p < 0.01$), **dTVV** = delta total vessel volume, **dPV** = delta plaque volume, **dLV** = delta lumen volume.

Table 2. Number of sub-segments with specific IVUS parameter in each patient.

Patient	Number of sub-Segments	IVUS Parameters							
		Tissue characteristic			Balloon-induced dissection		Pattern of remodeling		
		Hard	Soft	Normal	+	-	0	+	-
1	8	0	4	4	1	7	1	2	5
2	8	4	2	2	4	4	0	0	8
3	10	0	10	0	0	10	0	7	3
4	10	1	7	2	5	5	4	5	1
5	10	4	2	4	6	4	3	1	6
6	5	0	2	3	0	5	0	2	3
7	6	5	1	0	4	2	2	4	0
8	10	4	4	2	4	6	3	3	4
9	10	9	0	0	2	7	0	3	6
10	10	3	6	1	0	10	0	2	8
11	5	5	0	0	0	5	0	5	0
12	10	9	1	0	4	6	1	7	2
13	10	9	1	0	5	5	1	3	6
Total	111	53	40	18	35	76	15	44	52

REMODELING

Positive remodeling was observed in 52 sub-segments (46.8%), whereas negative remodeling occurred in 44 (39.6%). Both patterns of remodeling were observed along the entire injured segment in the majority of the patients (n=10) (table 2). Although sub-segments showing negative remodeling had a greater amount of residual plaque volume post-procedure, the increase in plaque volume was greater in those sub-segments with positive remodeling (figure 3). Indeed, sub-segments with negative remodeling showed a decrease in plaque volume.

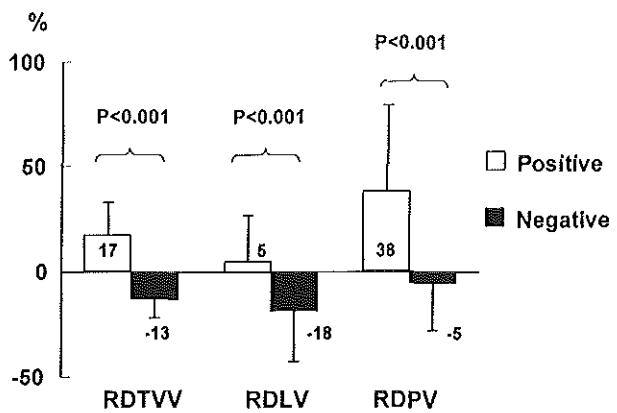

Figure 3. Comparison of relative changes in TVV, LV, and PV between sub-segments with negative (n=44) and positive (n=52) remodeling.
TVV = total vessel volume, **PV** = plaque volume, **LV** = lumen volume, **RDTVV** = relative delta total vessel volume, **RDPV** = relative delta plaque volume, **RDLV** = relative delta lumen volume

Table 3. Changes in IVUS parameters after 6 months.

Sub-segments	ΔTVV mm^3	Relative ΔTVV	ΔPV mm^3	Relative ΔPV	ΔLV mm^3	Relative ΔLV
All (n = 111)	0.31±4.9	0.028±0.18	1.9±4.25	0.175±0.38	-1.6±3.92	0.066±0.25
MLA site (n = 13)	-0.17±5.4	0.007±0.18	4.07±4.55	0.32±0.31	-4.25±4.25	0.258±0.26
MLL site (n=13)	-2.86 ±5.5	-0.068±0.19	3.24±5.47	0.354±0.55	-6.08±4.3	0.32±0.21

MLA = minimal lumen area, MLL = minimal lumen loss, TVV = total vessel volume; PV = plaque volume; LV = Lumen volume

MULTIVARIATE ANALYSES

Post-procedure IVUS predictors of both changes in total vessel volume and plaque volume are shown in table 4. Residual plaque volume had a negative influence on remodeling, whereas the presence of dissection had a positive effect on total vessel volume increase. Post-procedure lumen dimension volume was directly associated with plaque increase (table 4).

Table 4. Post-procedure IVUS predictors of changes in plaque volume and total vessel volume after 6 months.

IVUS parameters	Dependent variables					
	Delta plaque volume (n=111)			Delta total vessel volume (n=111)		
	p-value	Beta	95%CI	p-value	Beta	95%CI
Hard plaque composition	NS			NS		
Presence of dissection	NS			0.002	0.288	1.168: 4.969
Post-procedure PV	NS			0.001	-0.316	-0.391: -0.108
Post-procedure TVV	NS			NS		
Post-procedure LV	0.002	0.291	0.052: 0.225	NS		

PV = plaque volume; TVV = total vessel volume; LV = Lumen volume

Discussion

This study, assessing the local mechanism of restenosis by means of sub-segmental volumetric quantification of the entire injured vessel, shows the variability of both qualitative IVUS parameters and patterns of remodeling within the same target segment (table 2), as observed by Pasterkamp et al. in human femoral arteries.[27] Furthermore, in the majority (n=10) of the cases the site with maximal lumen loss was not the same as the site of the minimal lumen area at follow-up, and the mean distance between these two specific sites was 5.3 ± 4.8 mm. These findings may highlight the importance of analyzing the entire injured segment for the correct determination of the mechanism of restenosis in the future IVUS studies.

Our results also confirm that unfavorable remodeling is the major determinant of lumen loss (figure 2). Based on average values of changes in IVUS parameters (table 3), lumen loss after balloon angioplasty appears to be determined mainly by an increase in plaque volume. Similar results were found in two recent prospective studies.[7][28] The mean lumen loss in the balloon angioplasty group of the SURE trial[7] and the placebo group of the MVP study[28] were mainly due to an increase in plaque area. Contrasting, pioneer retrospective studies have described vessel shrinkage as causing 50-70% of lumen loss.[5][6] It should be taken into

account that average values may not represent the relative contribution of each component, remodeling and plaque growth, to lumen loss. Using linear regression, as suggested previously[24], we observed that lumen loss was actually determined by changes in vessel size (figure 2). Whereas change in total vessel volume was highly correlated with lumen loss in all analyzes, delta plaque volume was weakly related to delta lumen volume (figure 2).

Whether remodeling is an independent process or an adaptive response to compensate plaque growth is still debatable.[8][10] The correlation between changes in vessel size and plaque volume observed in the present investigation (figure 2) suggests that remodeling after balloon injury may represent an adaptive phenomenon as described by Glagov et al. in atherosclerotic plaques.[29] In fact, this correlation is both directions: segments with positive remodeling showed an increase in plaque volume, whereas those with vessel shrinkage had a plaque reduction (figure 3). Similar findings have been reported previously.[30] These studies may support the hypothesis that plaque retraction may be the ultimate determinant of negative remodeling.[31] However, it should be considered that other factors, such as inflammation[32] and shear or tensile stress[33], may exert an influence in both remodeling and plaque progression.

Local tensile stress, which is determined by lumen radius, may have stimulated plaque progression in sub-segments with large residual lumen maintaining the baseline shear stress, as suggested by Glagov et al.[33][34] Similarly, shear stress may be implicated in the negative correlation between residual plaque volume and vessel remodeling, and in the positive influence of dissection on vessel enlargement (table 4).[33] However, direct measurements of both tensile stress and shear stress in vivo are exceedingly complex and require sophisticated and laborious technology to draw any definitive conclusion.[35]

Dissection was detected by IVUS more frequently in sub-segments characterized as hard [36]. The previous hypothesis, based on angiographic studies, that non-occlusive residual coronary dissection has a favorable long-term outcome may be supported by the present IVUS study[37][38], since a positive influence of residual dissection on vessel enlargement was observed (table 4).

Plaque composition as characterized by IVUS was not correlated with any changes in IVUS parameters as reported by others.[5][6] Conversely, hard or calcific plaques have been implicated with negative remodeling in both atherosclerotic and restenotic lesions.[21][26][39] Methodological differences may explain diverging results, since these latter studies[21][26][39] did not assessed the influence of plaque composition on changes (delta) in IVUS parameters over time as performed in the other studies[5][6] and in the present investigation.

In summary, the findings of the present investigation, using 3-dimensional IVUS quantification of local changes in the vessel wall volumes, illustrates the complexity and variability of the arterial wall response to balloon injury and the importance of local factors (shear stress, growth factors, inflammation, degree of injury, etc) in this phenomenon.[2][40]

Limitations

The number of patients, similarly to all previous IVUS investigations[5][6], is a limitation of the present study. However, this is the first study employing a unique methodology to assess the local process of restenosis in 111 matched sub-segments injured exclusively by balloon inflation.

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CHAPTER 4

Three-Dimensional Intravascular Ultrasonic Volumetric Quantification of Stent Recoil and Neointimal Formation of Two New Generation Tubular Stents

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Three-Dimensional Intravascular Ultrasonic Volumetric Quantification of Stent Recoil and Neointimal Formation of Two New Generation Tubular Stents

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Currently, several different designs of coronary stents are available. However, only a few of the new generation stents have been investigated in large randomized trials. Mechanical behavior of first-generation stents (Palmaz-Schatz, Gianturco-Roubin) may not be applied to the new designs. We investigated the chronic mechanical behavior (recoil) of 2 stents recently approved by the Food and Drug Administration (MULTILINK and NIR). Forty-eight patients with single-stent implantation (23 MULTILINK and 25 NIR) were assessed by means of volumetric 3-dimensional intravascular ultrasound analysis after the procedure and at 6-month follow-up. In addition, volumetric assessment of neointimal formation was performed. No significant chronic stent recoil was detected in both groups (Δ MULTILINK stent volume: +5.6 ± 41 mm^3 [p = NS] and Δ NIR stent volume + 2.1 ± 26 mm^3 [p = NS]). A similar degree of neointimal formation at 6 months was observed between the 2 stents (MULTILINK 46 ± 31.9 mm^3 vs NIR 39.9 ± 27.6 mm^3, p = NS). In conclusion, these 2 second-generation tubular stents did not show chronic recoil and appeared to promote similar proliferative response after implantation in human coronary arteries. ©2000 by Excerpta Medica, Inc.

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It has been shown that stent design may influence the degree of neointimal formation in animal models.[1] Thus, the slow chronic expansion associated with self-expanding stents may yield a greater neointimal ingrowth in human coronary arteries.[2,3] Likewise, the negative clinical and angiographic results of a coil stent observed in a recent randomized study[4] comparing Cook GRII and Palmaz-Schatz stents may be influenced by the inability of this type of coil stent to prevent vessel remodeling.[5] Whether in vivo mechanical properties of the first generation of tubular stents (Palmaz-Schatz) could be applied to the recently designed tubular stents remains to be elucidated. Two second-generation balloon-expandable tubular stainless steel stents, MULTILINK (Guidant/Advanced Cardiovascular Systems, Santa Clara, California) and NIR (Boston Scientific, Maple Grove, Minnesota), have recently been approved for clinical use in the United States.[6] The aim of our study was to investigate the potential of chronic stent recoil and the degree of neointimal proliferation after implantation of these 2 stents.

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METHODS

From January 1998 to December 1998, 48 consecutive patients receiving either single MULTILINK or NIR (9-cell) stenting with intravascular ultrasound (IVUS) analysis after the procedure and at 6-month follow-up were eligible for this study. For 3-dimensional reconstruction, only patients investigated with IVUS imaging systems incorporating motorized transducer pullback at a constant speed of 0.5 mm/s were selected. All patients signed a written informed consent form. Before the procedure, clinical and angiographic characteristics (Table I) were similar between groups.

Stent deployment technique: Stent selection was based on operator preference. Stent size was selected to reach a 1.1 to 1.2 stent/artery ratio by quantitative coronary analysis. Stent length was chosen based on lesion length measured by quantitative coronary angiography to achieve complete lesion coverage. Thus, the distribution of stent lengths in the MULTILINK group was 8 mm (n = 1), 15 mm (n = 9), 25 mm (n = 12), and 35 mm (n = 1). In the NIR group the distribution of stent lengths was 9 mm (n = 2), 16 mm (n = 13), 25 mm (n = 7), and 32 mm (n = 3). Stents were delivered through 6Fr to 8Fr guiding catheters using 0.014-in guidewires. After predilatation of the target lesion, stents were deployed with subsequent high-pressure (14 to 20 atm) balloon postdilatation. All patients received aspirin (325 mg/day continuously) and ticlopidine (250 mg twice a day, maintained for 30 days) at least 24 hours before the pro-

TABLE I Baseline Characteristics

Variables	MULTILINK (n = 23)	NIR (n = 25)	p Value
Age (yrs)	61 ± 9	63 ± 9	0.39
Men	21 (91%)	22 (88%)	1.0
Diabetes mellitus	3 (13%)	4 (16%)	1.0
Unstable angina pectoris	10 (44%)	14 (56%)	0.47
Multivessel coronary disease	13 (57%)	10 (40%)	0.39
Left anterior descending coronary artery	9 (39%)	11 (44%)	0.78
Saphenous vein graft	1 (4%)	1 (4%)	1.0
Angiographic calcification (moderate or heavy)	6 (27%)	3 (13%)	0.28
Lesion type B2/C (ACC/AHA)	14 (61)	18 (72)	0.54
Quantitative coronary angiography			
Reference diameter (mm)	2.89 ± 0.48	2.78 ± 0.39	0.39
Lesion length (mm)	8.7 ± 3.7	8.2 ± 2.9	0.61
Minimal lumen diameter (mm)	0.94 ± 0.40	0.92 ± 0.37	0.83
Diameter stenosis (%)	67 ± 13	67 ± 12	0.95

cedure. Before the procedure, minimal lumen diameter, reference diameter, and percent diameter stenosis were calculated off-line in 2 orthogonal projections using an automated edge-detection system (CASS II, Pie Medical Imaging B.V., Maastricht, The Netherlands).

Three-dimensional intravascular ultrasound analysis: The use of a constant pullback speed at 0.5 mm/s during IVUS image acquisitions and 3-dimensional reconstruction with longitudinal viewing facilitated correct matches between postprocedure and follow-up images.[7,8] Precise identification of stent borders was also facilitated by the high echogenic characteristics of the stent struts.

Immediately after the procedure and at 6-month follow-up, IVUS was performed after administration of an intracoronary nitrate bolus. A single-element mechanical transducer (CVIS, Sunnyvale, California) was used in 70% of the patients in the MULTILINK group and in 64% of the NIR group, whereas a 64 multi-element electronic transducer (Endosonics Corporation, Rancho Cordova) was used in 30% and 36% of the patients, respectively (p = 0.8). After imaging acquisition, a complete IVUS run was recorded in s-VHS tape for off-line 3-dimensional reconstruction. All analyses were performed by an independent core lab (Cardialysis BV, Rotterdam, The Netherlands).

Three-dimensional IVUS reconstruction and quantitative volumetric analysis was performed using a Microsoft Windows-based contour detection system developed at the Thoraxcenter,[9] which permits analysis of up to 200 IVUS cross sections (slices). This program has been previously validated.[10] The system constructs 2 longitudinal sections from the data set and identifies the contours corresponding to the lumen, intima, media, or stent boundaries. Two longitudinal and 1 cross-sectional views are displayed, and corrections can be performed interactively by forcing the contour through visually identified points. Given the slice thickness of 200 μm, a total segment of 40 mm in length can be analyzed.

Volumetric data were calculated by the formula: $V = \Sigma^{n}_{i=1} A_i \cdot H$, where V = volume, A = area of external elastic membrane (EEM) or lumen or stent in a given cross-sectional ultrasound image, H = thickness of the coronary artery slice that was reported by this digitized cross-sectional IVUS image, and n = the number of digitized cross-sectional images encompassing the volume to be measured.[9] Measurements of neointimal hyperplasia volumes have been previously validated.[11] Volumetric analysis allowed the investigation of mechanical performance and neointimal proliferation of the entire stented segment (Figure 1).[7] The following postprocedure and 6-month follow-up measurements were compared: (1) stent = volume, symmetry index, and mean area; and (2) lumen = volume, mean area, and minimal cross-sectional area, and diameter. The volume and mean area of neointimal hyperplasia after 6 months were also calculated. Quantitative changes (Δ = follow-up–postprocedure measurements) were also calculated. After the procedure and follow-up, stent lengths were calculated by multiplying 200 μm (thickness of each IVUS image slice) by the number of slices (cross sections) within the stented segment.

Definitions: Stent symmetry index was calculated as the average of all stent symmetry indexes of each cross-section, which is defined as the ratio of minimal divided by maximal diameters.[12] A normal index is defined as a value $\geq$0.7.[12] Mean stent, luminal, and neointimal hyperplasia areas were automatically calculated as the average of all cross-section mean areas. Recoil was defined as a decrease in the stent volume at 6-month follow-up compared with postprocedure measurement. Neointimal hyperplasia was calculated as the difference between stent and luminal volumes at follow-up.

Statistical analysis: Statistical analysis was performed using the SAS 6.12 system. Continuous variables are expressed as mean ± SD. Comparisons between postintervention and follow-up measurements were performed with a 2-tailed paired *t* test. Comparisons between groups were performed using unpaired Student's *t* test. A p value of $<$0.05 was considered statistically significant.

RESULTS

IVUS measurements are listed in Table II. Both stents achieved similar postprocedural and follow-up volumes. No differences were observed in the mean stent or lumen areas. In addition, the symmetry index was similar between groups, with no deterioration of this index after 6-month follow-up in both stents.

Changes in the stent and lumen dimensions are illustrated in Figure 2. There were significant differences between postprocedure and follow-up lumen volumes in both MULTILINK (p $<$0.001) and NIR (p $<$0.001) groups. However, no recoil (postprocedure vs follow-up stent volumes) was demonstrated after 6 months in either group (Table II). The average stent

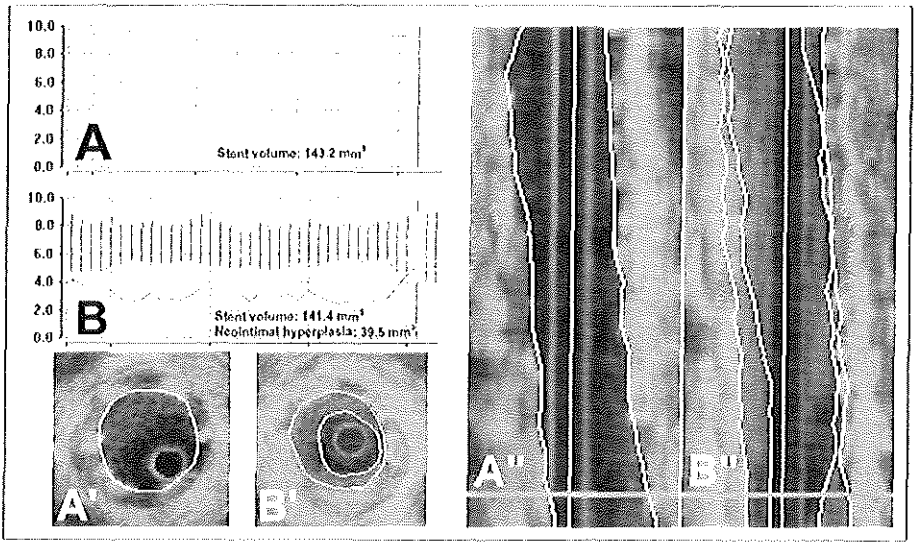

FIGURE 1. Standard display of the results by contour detection method. Charts on the *upper left panels* display the volumetric quantification of stent *(upper line)*, lumen *(middle line, chart B)*, and neointimal hyperplasia *(lower line, chart B)* immediately after stent implantation *(A)* and at follow-up *(B)*. Longitudinal reconstruction and minimal cross-sectional areas are depicted after the procedure (A', A'') and at follow-up (B', B'').

TABLE II Three-Dimensional IVUS Measurements

Measurements	MULTILINK (n = 23)	NIR (n = 25)	P Value
After procedure			
Symmetry index	0.9 ± 0.02	0.9 ± 0.03	0.89
Mean stent/lumen area (mm^2)	8.5 ± 2.1	8.5 ± 2.0	0.95
Minimal lumen area (mm^2)	7.0 ± 1.9	7.1 ± 1.9	0.85
Stent length (mm)	22.2 ± 10.2	18.5 ± 8.4	0.18
Stent/lumen volume (mm^3)	187 ± 96	155 ± 73	0.20
Follow-up			
Neointimal formation (mm^3)	46.0 ± 31.9	39.9 ± 27.6	0.49
Symmetry index	0.9 ± 0.03	0.91 ± 0.02	0.24
Mean stent area (mm^2)	8.75 ± 2.3	8.71 ± 2.0	0.95
Mean lumen area (mm^2)	6.6 ± 2.6	6.6 ± 1.7	0.95
Minimal lumen area (mm^2)	4.7 ± 2.1	4.9 ± 1.7	0.69
Stent length (mm^2)	22.0 ± 11.4	18.4 ± 9.5	0.20
Stent volume (mm^3)	193 ± 110	155 ± 74	0.18
Lumen volume (mm^3)	147 ± 100	116 ± 52	0.20

lengths measured with IVUS are also demonstrated in Table II, and no difference between postprocedure and follow-up was observed in both groups. Although, the average stent length was slightly longer in the MULTILINK group (p = NS) than in the NIR group, no difference in neointimal formation was observed between groups (Table II, Figure 1).

DISCUSSION

MULTI-LINK and NIR, 2 second-generation tubular stents, demonstrated similar postprocedural IVUS dimensions, which indicate equivalent radial force to acutely support the vessel wall resistance. Both stents had a good postprocedure symmetry index, demonstrating a homogeneous distribution of the radial force. Radial stiffness of MULTILINK and NIR stents has also been shown to be equivalent in an experimental (in vitro) study.[13]

No chronic stent recoil at 6-month follow-up was demonstrated in this 3-dimensional IVUS volumetric investigation. The symmetry index also remained unchanged after 6-month follow-up in both groups (Table II), which suggests that no localized stent recoil occurred. Because some studies using planar IVUS measurements showed that late recoil of Palmaz-Schatz stent rarely occurs,[14] tubular stents are believed not to recoil chronically. The inability of angiography to detect actual stent expansion may explain discordant results of previous studies concerning chronic recoil of Palmaz-Schatz stents.[15] For the first time, 3-dimensional IVUS with volumetric quantification, a new tool to investigate in vivo mechanical behavior of coronary stents, was used and confirmed the previous hypothesis that tubular stents do not recoil chronically.

Differences in designs and compositions of new tubular stents should be considered before grouping these stents in the same class. Investigations of the first-generation tubular stent (Palmaz-Schatz) should not be translated to the new tubular stent designs. A previous report has shown that Act-One (Vascular

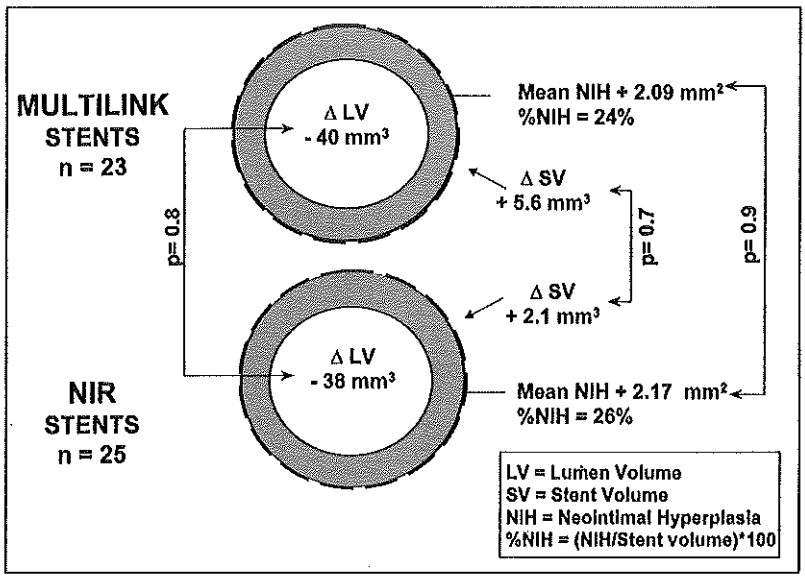

FIGURE 2. Chart illustrating quantitative changes (Δ) between postprocedure and follow-up measurements in the MULTILINK and NIR stent groups.

Therapies, Norwalk, Connecticut), a tubular nitinol stent with a design similar to the Palmaz-Schatz stent and with greater strut thickness (0.18 vs 0.065 mm), had higher recoil than the other tubular stents.[16]

Furthermore, in vitro studies have shown that some coil stents may have high radial stiffness, which contradicts the concept that coil stents have poor radial support.[13,17] In contrast, clinical investigations comparing the radial force of tubular and coil stents have shown contradictory results.[5,18] The mechanical behavior of coronary stents may differ between in vivo and in vitro situations because of elastic properties of the arterial wall, especially when diseased vessels are being investigated. Thus, further IVUS investigations should be encouraged to assess in vivo mechanical properties of new stent designs, because these may have an impact on vessel remodeling and neointimal formation after percutaneous interventions.

Lumen loss after either MULTILINK or NIR stent implantation was mainly caused by neointimal proliferation because both stents did not recoil after 6 months. In the 48 segments analyzed in our study, no difference in either neointimal hyperplasia volume or percentage of neointima formation was observed between the 2 groups. Neointimal formations observed with these tubular stents were comparable to those previously reported using different stents.[2,11]

The stainless steel tubular stents investigated in our study, MULTILINK and NIR, differ with respect to design (linked tubular wavy rings vs multicellular) and strut thickness (0.05 vs 0.1 mm).[19] Importantly, the neointimal proliferative response appears to be similar between both groups despite the theoretical rheologic advantage of the thinner strut thickness of the MULTILINK stent over the NIR stent. In contrast, both stents were able to maintain their volumes without change after 6 months (no chronic recoil), even though NIR stents have thicker struts than MULTILINK stents. In conclusion, these 2 second-generation tubular stents did not recoil chronically and appeared to promote an equivalent proliferative response after implantation in human coronary arteries.

Study limitations: IVUS imaging was performed after stent implantation, which limits the ability to detect coronary calcification. Thus, the assessment of coronary calcification in our study was made by angiography, which has some limitations. However, the influence of calcium on chronic stent recoil has not been demonstrated.

The assessment of acute recoil was not performed. Previous reports have investigated this issue using either angiography or conventional IVUS.[20,21] However, a small inaccuracy in these methods to detect acute stent recoil cannot be completely ruled out. Ideally, new systems incorporating the IVUS imaging element on the balloon/stent catheter would be helpful for assessing acute stent recoil.

Clinical and angiographic characteristics were similar between both stent groups. However, a randomized study may be required to eliminate any possible bias in the selection of stents, and to draw a more definitive conclusion about the proliferative response promoted by these stents.

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CHAPTER 5

Intracoronary Radiation Therapy: European Clinical Trials

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24. EUROPEAN CLINICAL TRIALS

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The pioneering work in the field of intravascular radiation therapy was originally carried out in Europe. In 1992, Liermann et al performed the first four cases of brachytherapy after femoral percutaneous angioplasty.[1] Subsequently, animal experiments carried out in the USA[2,3] and Europe[4] demonstrated the reduction of neointimal hyperplasia after endovascular radiotherapy. The insertion of a radioactive delivery catheter in human coronary arteries was performed for the first time by Condado et al in Venezuela.[5] As a result of these pioneering investigations, the first clinical trials were reported in 1997: in the USA, Teirstein et al demonstrated the effectiveness of gamma therapy for the treatment of in-stent restenosis,[6] whilst in Europe, Verin et al reported the feasibility of using beta sources after balloon angioplasty.[7]

In Europe, most of the trials have been carried out using beta-radiation sources, either with catheter-based systems or radioactive stents. Overall, the initial target has been the treatment of de novo coronary stenosis. However, recent design trials have included patients with restenotic lesions. This chapter summarizes the clinical trials carried out in Europe either as a part of larger trials designed in the USA or primarily designed in Europe.

Intracoronary radiation clinical trials using catheter-based systems

The clinical trials with catheter-based systems are summarized in Table 24.1. Initially, these trials were aimed at demonstrating the safety and feasibility of beta emitters in coronary arteries. Currently, results from the dose-finding and placebo-controlled trials are pending.

The GENEVA pilot clinical experience

This was the first feasibility study performed in Europe (Geneva, Switzerland) and also the first in the world to use intracoronary beta-radiation in humans.[7] A pure ^{90}Y beta-emitter source delivered via a centering catheter (Schneider Endovascular Radiation System, Schneider Worldwide, Büllach, Switzerland) was used to deliver 18 Gy at the surface of the balloon in 15 patients with de novo coronary stenoses treated with balloon angioplasty. At follow-up the restenosis rate was 40%. The investigators considered these to be unfavorable results owing to an insufficient dose administered at the adventitia (< 4 Gy).

Table 24.1 Intracoronary radiation clinical trials using catheter-based systems

Study (principal investigator)	*Design*	*Radiation system*	*Source*	*Prescribed dose*
GENEVA pilot study (V Venn/ Y Popowski)	Prospective, open- label	Schneider intravascular radiation system	^{90}Y wire (29 mm)	18 Gy to the inner arterial surface
Boston Scientific/ Schneider Dose-Finding Study (W Wijns)	Prospective, multi-center, randomized, dose-finding	Boston Scientific/Schneider intravascular radiation system	^{90}Y wire (29 mm)	9, 12, 15, and 18 Gy at 1 mm from the balloon surface
BERT 15 – European arm (PW Serruys)	Prospective, uncontrolled	Novoste system	^{90}Sr/^{90}Y seeds (30 mm)	Randomized 12, 14, 16 Gy at 2 mm from the source
Beta Cath (RE Kuntz)	Prospective, randomized, placebo-controlled, triple-masked	Novoste system	^{90}Sr/^{90}Y seeds (30 mm)	Randomized placebo or radiation (14 Gy in vessels ≥ 2.7 ≤ 3.35 mm and 18 Gy in vessels > 3.35 ≤ 4.0 mm) at 2 mm from the source
BRIE (PW Serruys)	Prospective, uncontrolled	Novoste system	^{90}Sr/^{90}Y seeds (30 and 40 mm)	14 Gy (≥ 2.5 ≤ 3.25 mm) or 18 Gy (> 3.25– ≤ 4.0 mm) at 2 mm from the source
START (JJ Popma)	Prospective, randomized, placebo-controlled triple-masked	Novoste system	^{90}Sr/^{90}Y seeds (30 mm)	Randomized placebo or radiation (16 Gy in vessels ≥ 2.7 ≤ 3.35 mm and 20 Gy in vessels > 3.35 ≤ 4.0 mm) at 2 mm from the source
START 40-20 (JJ Popma)	Prospective, control group of START will be used as control	Novoste system	^{90}Sr/^{90}Y seeds (40 mm)	16 Gy in vessels ≥ 2.7 ≤ 3.35 mm and 20 Gy in vessels > 3.35 ≤ 4.0 mm at 2 mm from the source
RENO (P Urban)	Prospective, surveillance registry	Novoste system	^{90}Sr/^{90}Y seeds (30 and 40 mm)	14–20 Gy after balloon, 16–22 Gy in stented pts, at 2 mm from the source
PREVENT (A Ratzner)	Prospective, randomized, blind	Guidant intravascular radiotherapy system/Nucleotron (afterloader)	^{32}P wire (27 mm)	Randomized 0, 28, 35, 42 Gy, at 0.5 mm into the vessel wall

Inclusion	*Population/ number of centers*	*Period*	*Primary end-point*	*Status/ results*
De novo lesions	15 pts/1 center in Switzerland	June 1995–November 1995	Feasibility and safety at 6 months	Completed — demonstrated safety and feasibility
De novo lesions	181 pts/ 5 centers in Europe	September 1997–September 1999	Angiographic criteria at 6 months	Interim results: dose-dependent reduction in the restenosis rate
De novo lesions	31 pts/ Rotterdam	April 1997–June 1998	Safety, feasibility and angiographic restenosis at 6 months	Completed — demonstrated safety and feasibility
De novo or restenotic lesions without a stent	1450 pts/55 sites in USA and 3 sites in Europe	July 1997–June 2000	TVR and MACE at 8 months	Enrollment phase
De novo or restenotic lesions without a stent in up to two vessels	350 pts (150 pts with single lesions and 100 with 2-vessel disease)/20 sites in Europe	July 1997–June 2000	TVR and MACE at 1 month and 6 months and 1 year. Angiographic criteria, aneurysm formation at 6 months	Enrollment phase
In-stent restenotic lesions	476 pts/49 sites in USA and 2 sites in Europe	September 1998–December 1999	TVR and MACE at 8 months	Follow-up phase
In-stent restenotic lesions	200 pts/25 sites in USA and 1 site in Europe	August 1999–August 2000	TVR and MACE at 8, 12, and 24 months and angiographic restenosis at 8 months	Enrollment phase
De novo or restenotic lesions up to three vessels	1000 pts/50 sites in Europe	April 1999	MACE at 6 months	Enrollment phase
De novo and restenotic lesions	50 pts/site in USA and 35 pts/site in Europe	February 1998–2000	Feasibility, safety and MACE at 1 and 6 months	Enrollment completed follow-up phase

Continued

Table 24.1 continued

Study (principal investigator)	Design	Radiation system	Source	Prescribed dose
INHIBIT (R Waksman)	Prospective, randomized, double-blind, sham-controlled	Guidant intravascular radiotherapy system/Nucletron (afterloader)	^{32}P wire (27 mm)	Randomized 0 or 20 Gy, at 1 mm into the vessel wall
DURABLE (PW Serruys)	Prospective, randomized, controlled, double-blind	Guidant intravascular radiotherapy system/Nucletron (afterloader)	^{32}P wire (27 mm)	16 Gy at 0.5 times reference diameter + 1 mm distance from the source
MARS (De Scheerder)	Prospective, registry	Mallinckrodt system	^{188}Re liquid-filled balloon (25 mm)	20 Gy at 0.5 mm into the vessel wall
GRANITE (PW Serruys)	Prospective, uncontrolled	Cordis gamma iRT™ delivery system	^{192}Ir seeds (23, 39, 55 mm)	14 Gy at 2 mm from the source

Intracoronary beta-radiation following PTCA for reduction of restenosis using the Boston Scientific/Schneider system: Dose-Finding Study

This multi-center, prospective, randomized, non-controlled study aimed to determine the effect of four different doses of beta-radiation, using the ^{90}Y pure beta-emitting source via a centering catheter (Schneider Irradiation Therapy System, Büllach, Switzerland) on coronary stenosis. In five European centers, 181 patients were randomized to receive 9, 12, 15, or 18 Gy at 1 mm tissue depth. The preliminary analysis demonstrated a dose-dependent reduction in angiographic restenosis with an extremely low restenosis rate in the 18 Gy arm: 8.3% in all patients (stented and treated with balloon alone) and 4.2% in patients treated with balloon alone (V Verin, personal communication, Congress of the European Society of Cardiology Barcelona, August 1999). Final results will be available by November 1999.

BERT 1.5 (Beta Energy Restenosis Trial—1.5): the Rotterdam experience

BERT 1.5 stands for the European arm of the BERT trial. This trial was conducted at the Thoraxcenter in Rotterdam in 31 patients from April 1997 to June 1998. This feasibility study was designed to test the ^{90}Sr/^{90}Y source in

Inclusion	*Population/ number of centers*	*Period*	*Primary end-point*	*Status/ results*
In-stent restenotic lesions	360 pts/USA and Europe	August 1998	TLR, death or Q-MI at 9 months	Enrollment phase
De novo or restenotic lesions (≥ 1 lesion)	900 pts/9 centers in The Netherlands	October 1999	MACE at 1 year	Approval phase
De novo lesions	35 pts/2 centers (Belgium, The Netherlands)	November 1998–March 1999	Feasibility and safety at 6 months	Enrollment completed
In-stent restenotic lesions	120 pts/11 sites in Europe and 1 in Australia	June 1999–February 2003	Angiographic criteria, MACE, safety at 6 and 36 months	Enrollment phase

a hydraulic system (Beta-Cath™ system, Novoste Corporation, Norcross, GA, USA). The dose was randomized to 12, 14 or 16 Gy prescribed at 2-mm depth from the source axis. Twenty-three patients were treated with balloon angioplasty, whereas eight patients received a stent after radiation. Delivery of radiation was successful in all patients but one. At 6 months, the restenosis rate was 28% and target vessel revascularization 23%. Two thrombotic occlusions in patients receiving a stent after radiation were observed at the 2.5- and 10-month follow-up.[14]

Beta-Cath Trial

This prospective, randomized, placebo-controlled trial aims to evaluate the safety and effectiveness of the $^{90}Sr/^{90}Y$ source (Beta-Cath™ system) versus placebo in de novo and restenotic lesions of native coronary arteries. Three centers in Europe are participating in this trial. Complete 8-month follow-up data will be available in 2000.

BRIE Trial (Beta Radiation in Europe)

This non-randomized trial is designed to evaluate the safety and performance of the $^{90}Sr/^{90}Y$ source (BetaCath™ system) in de novo and restenotic lesions of native coronary arteries up to two vessels. This study is being carried out only in Europe (20 sites). Complete 8-month follow-up data will be available in 2000.

START Trial (STents And Radiation Therapy)

This prospective, randomized, placebo-controlled trial aims to evaluate the safety and performance of the $^{90}Sr/^{90}Y$ source (Beta-Cath™ system) in the treatment of in-stent restenosis of native coronary arteries. Two sites in Europe are involved in this study. The enrollment phase will be completed by the end of 1999. One site in Europe will be involved in the START 40-20 Trial, which is designed to assess the feasibility and efficacy of the 40-mm long $^{90}Sr/^{90}Y$ source for the treatment of in-stent restenotic lesions.

RENO Trial (European surveillance Registry with the Novoste Beta-Cath™ system)

This prospective multi-center, multi-national surveillance registry is designed to assess the clinical event rate of $^{90}Sr/^{90}Y$ source (Beta-Cath™ system) combined with approved PTCA techniques (balloon angioplasty, rotablator, laser, and stenting) in patients with coronary artery disease (native or bypass grafts). This study is being carried out only in Europe (50 sites) and multi-vessel treatment up to three vessels is allowed.

PREVENT (Proliferation REduction with Vascular ENergy Trial)

Prospective, randomized, blinded, multi-center study aimed to determine the safety of the Guidant (Santa Clara, CA) beta-radiation system in human coronary arteries following PTCA or stent implantation. The system consists of a ^{32}P 27-mm source wire, a centering spiral balloon and an automatic computerized afterloader (Nucletron BV, Waardgelder, Veenendaal, The Netherlands). The enrollment phase has been completed in Europe and 6-month angiographic and clinical follow-up data are expected by the first quarter of 2000.

INHIBIT (INtimal Hyperplasia Inhibition with Beta In-stent Trial)

A randomized, multi-center, double-blind, sham-controlled study started in the USA and Europe to demonstrate the clinical safety and efficacy of the Guidant beta-radiation system for treatment of in-stent restenosis. The enrollment phase will be completed by the end of 1999 and 9-month angiographic and clinical follow-up will be available by the end of 2000.

DURABLE Trial (DUtch RAndomized Brachytherapy study for Long-term evaluation of Efficacy)

This randomized, placebo-controlled, double-blind study is aimed to assess the effect of brachytherapy by means of the Guidant intravascular brachytherapy system, after optimal balloon angioplasty (stenosis diameter $< 35\%$), elective stenting, and indicated stenting (bail-out and suboptimal result) in patients with multi-vessel stentable lesions (up to two vessels) with

respect to MACE-free survival at 1 year. Nine hundred patients will be randomized in nine centers in The Netherlands. The enrollment phase started in October 1999.

MARS (Mallinckrodt Angioplasty Radiation Study)

This is the first European prospective registry to assess the feasibility and safety of the ^{186}Re liquid-filled balloon (Mallinckrodt System) for the treatment of de novo coronary lesions. Results at the 6-month follow-up will be available by the end of 1999.

The GRANITE Study (Gamma-Radiation to Atheromatous Neointima using Intracoronary Therapy in Europe)

This is the first trial utilizing gamma-radiation for the treatment of coronary in-stent restenosis in Europe. Patients will be followed up for 3 years at 11 sites in Europe including France, Germany, Italy, and The Netherlands, as well as one site in Australia. The radiation system (Gamma IRT™ Delivery System, Cordis, Miami, FL) consists of a ribbon of radioactive ^{192}Ir seeds (up to 55 mm in length) that will be delivered to the target lesion via a delivery catheter with a closed end lumen and using a hand-cranked containment/delivery device. The radioactive ribbon will be left at the angioplasty site for between 15 and 25 min to deliver the prescribed dose.

Intracoronary radiation clinical trials using radioactive stents

The clinical trials utilizing radioactive stents have demonstrated safety and effectiveness in preventing neointimal proliferation in a dose-related manner. However, a new phenomenon has become evident: restenosis at the edges of the high activity radioactive stent, coined the 'candy wrapper' effect.[8] The clinical trials using radioactive stents are summarized in Table 24.2.

IRIS Trial (Isostent for Restenosis Intervention Study)

This feasibility registry involved three centers in Europe in which 40 radioactive stents with an activity of 0.75–1.5 μCi were implanted. This trial demonstrated feasibility and safety with a restenosis rate that ranged between 17% (Rotterdam)[9] and 50% (Milan).[10]

European ^{32}P Dose–Response Study

This dose-finding study is being conducted in five centers in Europe. Radioactive stents of four ranges of activity have been utilized: 1.5–3.0;

Table 24.2 Intracoronary radiation clinical trials using radioactive stents

Study (principal investigator)	*Design*	*Radiation system*	*Source*	*Prescribed dose*
IRIS Trial Europe (J Moses)	Prospective, non-randomized	Isostent	^{32}P impregnated Palmaz-Schatz or BX stents (15 mm)	0.75–1.5 μCi
European ^{32}P Dose-Response Study (J Moses)	Prospective, non-randomized	Isostent	^{32}P 15-mm Fischell BX stent	1.5–3.0 μCi, 3.0–6.0 μCi, 6.0–12 μCi, and 12–20 μCi
Cold End Study (J Moses)	Prospective, non-randomized	Isostent	^{32}P 25-mm Fischell BX stent	3–24 μCi in mid 15.9 mm, cold ends 5.7 mm both edges
Hot End Study (J Moses)	Prospective, non-randomized	Isostent	^{32}P 18-mm Fischell BX stent	4.5–9 μCi total activity in mid 14 mm, 2-mm hot ends 1.3–2.6 μCi/mm

3.0–6.0; 6.0–12; and 12–20 μCi. The Milan group ($n = 82$ patients) reported a suppression of the neointimal hyperplasia in a dose-related manner (between 1.5 and 12 μCi). Edge restenosis ('candy wrapper') was observed in 36% for 1.5–3.0 μCi, 38% for 3.0–6.0 μCi, and 50% for 6.0–12-μCi activity levels.[10] Currently, the Milan group is evaluating the use of stent activities up to 20 μCi.,The Heidelberg group enrolled 11 patients for radioactive stent implantation of activity levels between 1.5 and 3.0 μCi. Target vessel revascularization was 36%, mainly at the articulation of the Palmaz–Schatz stent.[11] In Rotterdam, 40 patients have been evaluated after 6.0–12.0-μCi radioactive stent implantation. To date, 18 patients have returned for angiographic follow-up. No restenosis (> 50% diameter stenosis) was observed within the stent. However, at the edges of the stent the restenosis rate reached 55%, leading to target vessel revascularization in 30% of the patients (AJ Wardeh, personal communication). Data from the Vienna experience will be available at the end of 1999.

Two trials have been designed to address the problem of edge restenosis. The **Cold End Study** is aimed to determine the efficacy and safety of the ^{32}P 25-mm Fischell BX stent, of which both 5-mm ends are inactive ('cold

Inclusion	*Population/ number of centers*	*Period*	*Primary end-point*	*Status/ results*
De novo or restenotic lesions	40 pts/3 centers (Milan, Rotterdam, Hanover)	September 1997–October 1998	Safety and efficacy on prevention of restenosis at 4–6 months	Completed: demonstrated feasibility and safety
De novo or restenotic lesions	200 pts/5 centers (Milan, Heidelberg, Rotterdam, Aalst, Vienna)	June 1997–ongoing	Safety and efficacy on prevention of restenosis at 4–6 months	Reduction of pure intra-stent restenosis in dose- response manner. Stent edge restenosis ≥ 3 μCi
De novo or restenotic lesions	38 pts/3 centers (Rotterdam, Milan, Aalst)	May 1999–ongoing	Safety and efficacy on prevention of restenosis in-stent and at edges at 6 months	Enrollment phase
De novo or restenotic lesions	60 pts/4 centers (Rotterdam, Milan (2 sites), Vienna)	August 1999–ongoing	Safety and efficacy on prevention of restenosis in-stent and at edges at 6 months	Enrollment phase

ends'). Conversely, the **Hot End Study** is aimed to determine the efficacy and safety of the ^{32}P 18-mm Fischell BX stent, of which both 2-mm ends present with higher activity ('hot ends') as compared with the inner 14 mm, which has a total activity ranging from 4.5 to 9 μCi. These two studies are still in the enrollment phase.

Conclusions and future perspective

The use of endovascular beta-radiotherapy in Europe demonstrated that this therapy is safe and feasible. Furthermore, preliminary results of a dose-finding study with the Boston Scientific/Schneider system have been very promising (V Verin, personal communication). This beneficial effect of radiation in preventing restenosis may be explained partially by the positive influence of brachytherapy on the remodeling process.[12,13] However, some detrimental clinical consequences of intracoronary radiation may also be recognized from the European experience. The edge effect, also named 'candy wrapper effect', was

reported by Albiero et al after radioactive stent implantation.[10] Further, the occurrence of late coronary thrombosis has been associated with radiotherapy.[14] This phenomenon may be the consequence of delayed endothelialization, persisting dissections[15] or the inability of tubular stents to follow vessel enlargement promoted by radiation leading to late stent malapposition.[16]

Potential solutions for these problems include the use of new designs of radioactive stents or hybrid techniques (catheter-based + radioactive stent)[17] in addition to the use of prolonged antithrombotic therapy. Also, the avoidance of conventional stent implantation may be considered in the setting of catheter-based endovascular radiotherapy.

There are still several unanswered questions which should be resolved before determining the potential of this new technique. First, the use of beta or gamma 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. Equally, the clinical effect of the dose-rate (radioactive stent—low dose-rate versus catheter-based radiation—high dose-rate). Finally, the target tissue must be defined, as well as the minimal effective dose to be delivered. Hopefully, after the completion of ongoing trials in Europe, as well as in the USA, many of these issues will be answered.

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CHAPTER 6

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

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Abstract

Objectives: The aims of the study were to determine the incidence of relocation of the minimal luminal diameter (MLD) after ß-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 pre-intervention, 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, 4 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% versus 26.3%; $p<0.0001$). The rate of >50% diameter stenosis differed between the 4 pre-defined 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.

Introduction

During the past 10 years the efficacy of percutaneous interventions in preventing restenosis after percutaneous interventions 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, as well as possessing a better inter- and intraobserver 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 (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 non-radiation studies unfair. This study was aimed to (1) determine the incidence of the relocation of the MLD after ß-radiation therapy following successful BA and, (2) describe a new methodological approach to accurately analyze and report 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 ß-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 ß-emitting ^{90}Y and patients were randomized to receive doses of 9,12,15, or 18 Gray (Gy) at 1mm 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 4 interconnected compartments which allows centering of the source lumen relative to the arterial lumen, and (3) a computerized afterloader which allows automated advancement and positioning of either the dummy or the active source (14).

QCA analysis and definitions

QCA analysis was performed off-line by an independent corelab (Cardialysis, Rotterdam, the Netherlands). 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 (4,15-16). The area of interest was selected after reviewing all cinefilms performed during the index procedure. Any angiographic sequence showing the lesion pre-intervention, positions of angioplasty balloon, and 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 and angioplasty balloon relative to the original lesion. The analyst defined a coronary segment bordered by angiographically visible sidebranches which encompassed the original lesion, angioplasty balloon and radiation source. This segment was defined as the *vessel segment (VS)*. (figure 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 were filmed in the same projections as performed previously. The proximal sidebranch within the VS was used as an index anatomical landmark. 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 were computed by the CAAS software. 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)*.

CAAS software. 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 2 tungsten markers defined the *irradiated segment (IRS)*. (figure 1) All regions of interest were superimposed on the pre-, post-procedural and follow-up angiograms. *Geographical miss* was defined for those cases where the entire length of the injured segment 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 enabled relocation of the MLD to be defined (figure 2). *Relocation pre-post* was defined as those cases where the MLD of the VS post-treatment was located in a different subsegment in the 2 orthogonal projections from that of the index procedure. *Relocation post-fup* was defined as those cases where the MLD of the VS at follow-up was located in a different subsegment in the 2 orthogonal projections from that post-procedure. *Relocation pre-fup* was defined as those cases where the MLD of the VS at follow-up was located in a different segment in the 2 orthogonal projections from that at the index procedure (figure 2).

Additionally, the analyst computed the MLD in every region of interest and calculated the acute gain, late loss and the frequency of >50% diameter stenosis on a regional basis. Acute gain was defined as MLD post-treatment minus MLD pre-intervention. Late loss was defined as MLD post-treatment 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) presenting with matched views and correct angiographic documentation, was used as the control group. VS, TS and relocation of the MLD were defined in this cohort as above described.

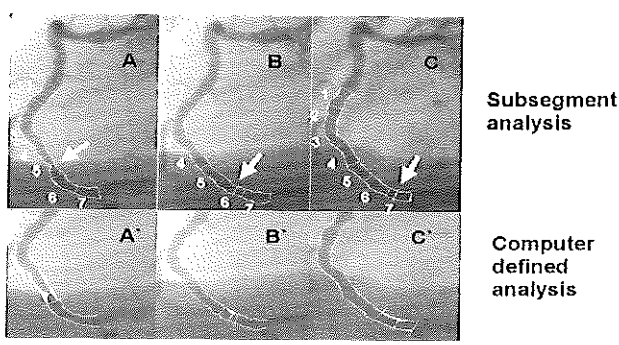

Figure 1
A. Target segment (TS) is between proximal and distal margin of the target lesion automatically defined by the quantitative coronary angiography system. Vessel segment (VS) is bordered by visible sidebranches, which encompass the target segment (TS), and the position of the angioplasty balloon 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 2 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.

Statistical analysis

Data are presented as mean ± standard deviation or proportions. To compare qualitative variables, the Chi-square test was carried out. To compare quantitative variables, the Student's 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 ß-radiation were eligible for the study. By comparing the technician worksheet with the angiograms recorded, the analyst was able to identify those patients in whom all balloon inflations and source positioning were filmed and all target views were matched. Using this systematical approach, 65 patients who did not accomplish these technical requirements to perform 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 prescirbed (9,12,15, or 18 Gray (Gy) at 1mm 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 the table 1. No differences were observed between the 2 groups.

Table 1. Baseline Characteristics

	Dose-Finding Group (n=65)	**Control Group (n=179)**
Age, years	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 indicates Gray.

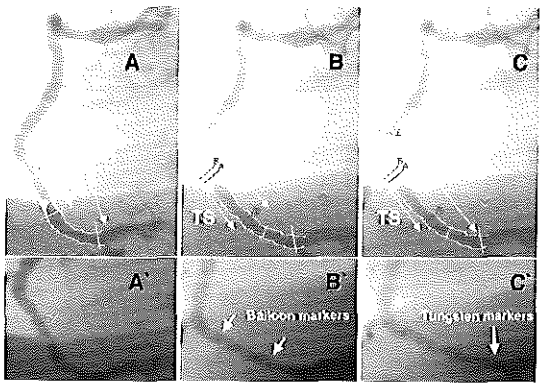

Figure 2
A. Subsegmental analysis before procedure. Vessel segment (VS) was automatically divided into 5-mm subsegments by the CAAS II system. The original lesion is located at segment No.5 pre-procedure as the arrow indicates. A'' Computer defined analysis pre-procedure. B. Subsegmental analysis at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

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 pts (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 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 2 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 the 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 indicates injured segment; IRS indicates irradiated segment.

Methodological implications of the relocation of the MLD

QCA data derived from the analysis of the pre-defined regions are presented in the table 3.

Table 3. QCA data from the 4 pre-defined 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 indicates diameter stenosis; fup indicates follow-up; INS indicates injured segment; IRS indicates irradiated segment; MLD indicates minimal luminal diameter; pre indicates pre-intervention; post indicates post-intervention; TS indicates target segment; VS indicates vessel segment.

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 demonstrated also a notable incidence of relocation. This phenomenon noted after radiation was witnessed in previous studies that showed 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 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 previous radiation trials and the poor clinical outcome (i.e., high target vessel revascularization rates) observed in these studies (22).

Further, as changes in the reference diameter may occur during the follow-up period, the use of the percent diameter stenosis measurements is questioned as an accurate estimate of lesion severity (19,20). In this regard, 2 thirds of our study population demonstrated an increase in the value of the pre-intervention 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 intravascular ultrasound 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 pre-existing plaques which became angiographically apparent or progressed after the treatment and tapering of the vessel may have accounted for the relocation of the MLD. On top of 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 pre-defined 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 which was injured by the angioplasty 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 in 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 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 pre-intervention. The meticulous analyses proposed are likely to give 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 endpoint, 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).

Limitations

The definition of relocation of the MLD depends decisively on the accurate documentation of all steps followed during the procedure. This was accomplished only in 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 the potential and limitations of this new technique.

Appendix

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

University Hospital, Geneva, Switzerland (57): Verin Vitali, MD, Youri Popowski, MD, Delafontaine Patrice, MD, Kurtz John, MD, Papirov Igor, PhD, Sergey Airiian, MD, Philippe Debruyne, MD, Ramos de Olival Jose, MD.

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University Hospital, Essen, Germany (26): Baumgart Dietrich, MD, Sauerwein Wolfgang, MD, Erbel Raimund, MD, von Birgelen Clemens, MD, Haude Michael, MD.
University Hospital, Kiel, Germany (22): Lins Markus, MD, Simon Ruediger, MD, Kovacs Gyorgy, MD, Thomas Martin, MD, Herrmann Gunhild, MD, Wilhelm Roland, MD, Kohl Peter, MD.
Kings College Hospital, London, United Kingdom (22): Thomas Martin, MD, Calman Francis, MD, Lewis Niel, PhD.

Data Monitoring: Thaler Thomas, MD (Boston Scientific)

Angiographic Core-Laboratory and Data Analysis:
Teunissen Yvonne, PhD, (Clinical Trial Manager), Spierings Astrid, Van derWiel Connie, Kloek Gitte, MSc, Disco Clemens, PhD
Critical Events Committee: Dekkers Jaap, MD, Serruys Patrick, MD, PhD.

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CHAPTER 7

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%)

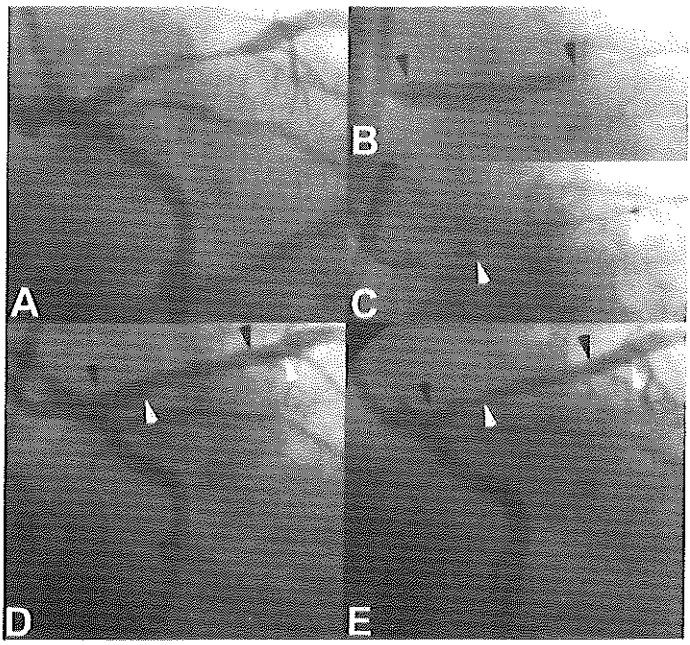

Figure 1. Geographic miss induced by balloon dilatation. A, Lesion located in proximal segment of left anterior descending coronary artery. B, Balloon dilatation performed during intervention (black arrowheads indicate area injured by balloon). C, Radiation source train in place. Irradiated area is delimited 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.

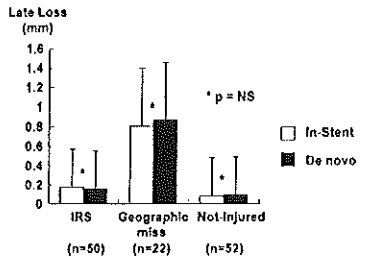

Figure 2. Difference in late loss between IRS, geographic miss edges, and uninjured edges. De novo lesions and in-stent restenosis demonstrated same degree of late loss between 3 groups.

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 8

The Effect of ^{32}P Beta-Radiotherapy on Both Vessel Remodeling and Neointimal Hyperplasia after Coronary Balloon Angioplasty and Stenting. A Three-dimensional Intravascular Ultrasound Investigation.

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The Effect of ^{32}P Beta-Radiotherapy on Both Vessel Remodeling and Neointimal Hyperplasia After Coronary Balloon Angioplasty and Stenting: A Three-Dimensional Intravascular Ultrasound Investigation

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ABSTRACT: Intracoronary radiation is a promising therapy to decrease restenosis after percutaneous intervention. The aim of this pilot study was to determine the mechanism of intracoronary beta-radiation after balloon angioplasty and stenting in a double-blind placebo-controlled randomized fashion. Twenty-six patients were randomized to either placebo (n = 6) or 3 doses (28, 35 and 42 Gy) of beta-radiation (n = 20) using the Guidant brachytherapy system (27 mm long ^{32}P source wire). Of these, 21 patients underwent post-procedure and 6-month follow-up three-dimensional intravascular ultrasound (IVUS) assessment. Volumetric quantification was performed by means of a semi-automated contour detection system after an ECG-gated motorized pullback IVUS imaging and three-dimensional reconstruction. We compared the volumetric changes (Δ) of total vessel volume (TVV), plaque volume (PV) and lumen volume (LV) after 6 months between placebo (dummy wire) and irradiated patients. In addition, the volume of neointimal hyperplasia was quantified within the stented segments. There was an opposite behavior of TVV and LV change between placebo (ΔTVV = -24 mm³ and ΔLV = -42 mm³) and irradiated (ΔTVV = +18 mm³ and (ΔLV = +5 mm³) patients. The mean neointimal formation within the stented segment in the irradiated patients (n = 7) was 1.9 mm³ (1.5%). Our results suggest that beta-radiation affects vessel remodeling after percutaneous intervention and inhibit neointimal formation in stented patients.

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Key words: brachytherapy, neointimal hyperplasia, remodeling

Restenosis after percutaneous intervention has been reduced with the advent of coronary stents.[1,2] However, further reduction in the incidence of restenosis appears to be difficult using conventional approaches.

The introduction of intravascular ultrasound (IVUS) in the clinical practice has refined our knowledge about the mechanism of restenosis. Thus, the restenotic process can be divided in two major components: vessel remodeling and neointimal formation. The former predominates after balloon angioplasty (BA), whereas the latter is the main cause of in-stent restenosis.[3,4]

Intracoronary radiation is a promising therapy to decrease restenosis after percutaneous intervention. Stimulated by animal studies showing inhibition of neointimal formation by radiation,[5–7] two randomized trials have shown the reduction of restenosis by treating restenotic lesions with gamma radiation.[8,9] Further, a non-randomized study has shown the safety and feasibility of beta radiation, with a satisfactory (15%) rate

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of restenosis in *de novo* lesion treated with balloon angioplasty.[10]

Recent IVUS investigations suggested that beta radiation after BA may affect vessel wall remodeling.[11-13] These findings have been corroborated by some experimental studies.[14,15] However, the relative contribution of radiation on vessel remodeling and neointimal formation remains to be clarified.

The aims of this pilot study were: 1) to assess the effects of beta radiotherapy on coronary segments successfully treated by BA or stenting; and 2) to compare the behavior of irradiated and non-irradiated (sham) coronary segments 6 months after treatment by means of a volumetric three-dimensional (3-D) IVUS assessment.

METHODS

Patient selection. In this double-blind feasibility and safety study, 26 patients were randomized to either sham (placebo) or 3 different doses of beta-radiation (28, 35 or 42 Gy, as calculated at 0.5 mm into the vessel wall). The Medical Ethics Committee of the University Hospital Dijkzigt has approved the use of intracoronary radiation. All patients gave written informed consent.

Radiotherapy system. The Guidant Brachytherapy System (Guidant Corporation, Santa Clara, California) used in this study includes a 0.018" nitinol wire with 27 mm of ^{32}P source at its tips. The use of a centering spiral balloon (27 mm long) allows the administration of prescribed dose homogeneously in the vessel wall as well as distal vessel perfusion during balloon inflation at a maximum inflation pressure of 4 atmospheres (atm). Automated source delivery unit controls dose delivery and source withdrawal, providing "hands-off" radiation delivery.[16] The duration of the treatment and dose necessary to reach 0.5 mm into the vessel wall are calculated using the mean reference vessel diameter by IVUS immediately prior to radiation delivery.

IVUS analysis system. The segment subject to 3-D reconstruction was examined with a mechanical IVUS system (ClearView, CVIS, Boston Scientific Corporation, Maple Grove, Minnesota) with a sheath-based IVUS catheter incorporating a 30 MHz single-element transducer rotating at 1800 rpm (Ultracross, CVIS). An ECG-gated image acquisition and digitization was performed by a workstation designed for the 3-D reconstruction of IVUS images (EchoScan, Tomtec, Munich, Germany).[18] IVUS images were acquired coinciding with the peak of the R wave, which eliminates the artifacts caused by the movement of the heart during the cardiac cycle. Then, the IVUS transducer was withdrawn every 0.2 mm to acquire the next image coincident to the R-wave.[17]

A Microsoft Windows™-based contour detection program, developed at the Thoraxcenter, was used for the 3-D volumetric quantification.[18] The feasibility and intra- and inter-observer variability of this system have been validated in clinical protocols.[19,20] Briefly, this program constructed longitudinal sections from the data set and identified the contours corresponding to the lumen and media and stent boundaries. Careful checking and editing of the contours of the planar images were performed by two independent experts who were blinded to the treatment assignments.

Volumetric data were calculated by the formula: $[V = \sum_{i=1}^{n} Ai * H]$, where V = volume, A = area of external elastic membrane (EEM), 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-sectional IVUS image, and n = the number of digitized cross-sectional images encompassing the volume to be measured.[18]

The methodology to define the treated segment has been previously described.[13] Angiogram was performed after positioning the radioactive source in the centering balloon and the relationship between anatomical landmarks and the two radiopaque markers of the radiation source were noted after contrast injection (Figure 1). Typically, the aorto-ostial junction and the side-branches were used as landmarks. The anatomical landmark closest to either of the source markers was used as a reference point. During the subsequent IVUS imaging pullback, this reference point was recognized and used for selecting the area of interest: 27 mm for the irradiated segment analysis. In a separate analysis we selected only the segment covered by stents within the irradiated area. This was facilitated by the highly echogenic characteristics of the stent struts. At follow-up, correct matching of the region of interest was performed by comparing the longitudinal reconstruction to that post-procedure (Figure 2).

Procedure. All patients received aspirin (250 mg/day) and intravenous heparin (10,000 IU) before the procedure and stented patients also received ticlopidine (250 mg/day). Heparin was given to maintain the activated clotting time > 300 seconds. BA and stenting were performed according to standard clinical practice. In the stented patients, high-pressure post-balloon inflation was performed guided by IVUS. The diameter of the centering balloon was chosen based on IVUS mean reference vessel size (average of the mean distal and proximal reference diameters). This measurement was performed after optimization of the results of balloon angioplasty or stenting. Thus, the centering balloon was placed in the target segment and inflated to 4 atm. After testing the perfusion of the distal coronary segment and checking the correct location of the centering balloon

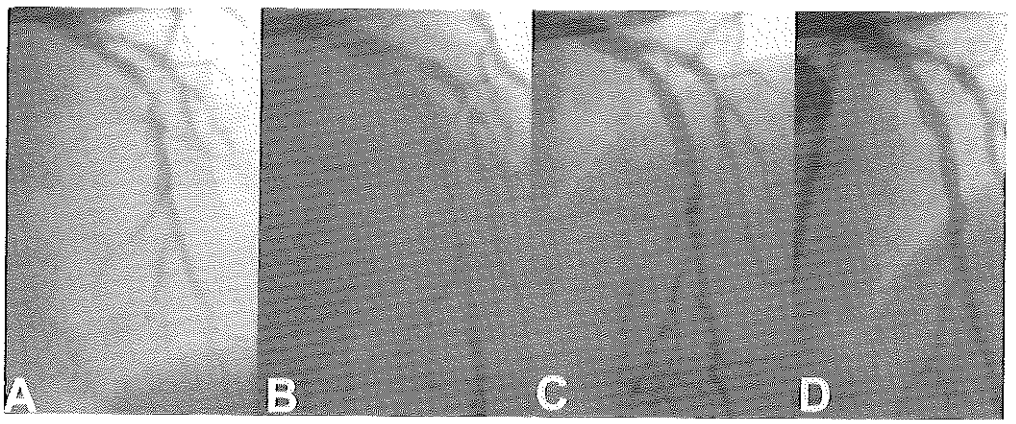

Figure 1. *(A) Pre-procedure angiogram of the left anterior descending artery (LAD); (B) Angiogram to verify the correct position of the spiral centering balloon and source wire. Distal perfusion is also confirmed as well as the anatomical landmarks for 3-D IVUS reconstruction of the irradiated segment; (C) Post-procedure angiogram of the LAD demonstrates good angiographic result; (D) Six-month follow-up angiography without restenosis.*

by contrast injection (Figure 1), the radioactive or "dummy" source wire (27 mm) was placed in the centering balloon by means of the automatic delivering system. Afterwards, repeat angiography and IVUS pullback were carried out. A continuous motorized pullback at a speed of 0.5 mm/second was first carried out, followed by an ECG-gated pullback at a stepwise of 0.2 mm/step. Intracoronary nitrates were administered immediately prior to each of the IVUS pullbacks. At 6-month follow-up, further IVUS analysis of the treated area was performed.

Quantitative 3-D IVUS analysis. The following volumetric measurements were obtained: total vessel (EEM) and lumen. Plaque volume was automatically calculated by subtracting lumen volume from the total vessel volume.

In stented patients, after selecting only the segment covered by stent, we also calculated neointimal hyperplasia, which was calculated by subtracting lumen volume from stent volume. *In vivo* measurement of neointimal formation after stenting has been previously validated.[21] Plaque volume outside the stent was also calculated by subtracting stent volume from total vessel volume within the stented segments. The assessment of EEM in stented patients has been reported.[22] Although in this previous report the delineation of EEM was not possible in some patients due to the stent shadowing, in our study the delineation of EEM boundary was possible in all stented patients. 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 3-D reconstruction with multiple longitudinal views facilitates the visualization of vessel structures outside the stent. In all cases, the stented segment was covered by the radiation or dummy source wire.

In order to assess the volumetric changes of the vessel structures after 6 months, the delta value for each measurement was calculated (delta (Δ) = follow-up – post-procedure).

Statistical analysis. Quantitative data are presented as mean ± standard deviation. The comparisons between the volumetric data of placebo versus irradiated patients and stent versus BA patients (in the irradiated group) were performed using an unpaired Student's t-test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

All patients have completed 6-month clinical follow-up. Of these, 5 patients (1 placebo) did not undergo IVUS at 6 months: 2 irradiated patients presented subacute thrombosis, one presented late (3 months after the procedure) thrombotic occlusion and another irradiated patient had a severe restenotic lesion demonstrated by angiography. The lesion was located in an area not covered by radiation, proximal to the irradiated site where a balloon was inflated to treat a proximal dissection. Thus, only a manual IVUS pullback was performed in this patient prior to reintervention. The non-irradiated patient was asymptomatic with a negative stress test at the time of follow-up but refused angiographic restudy.

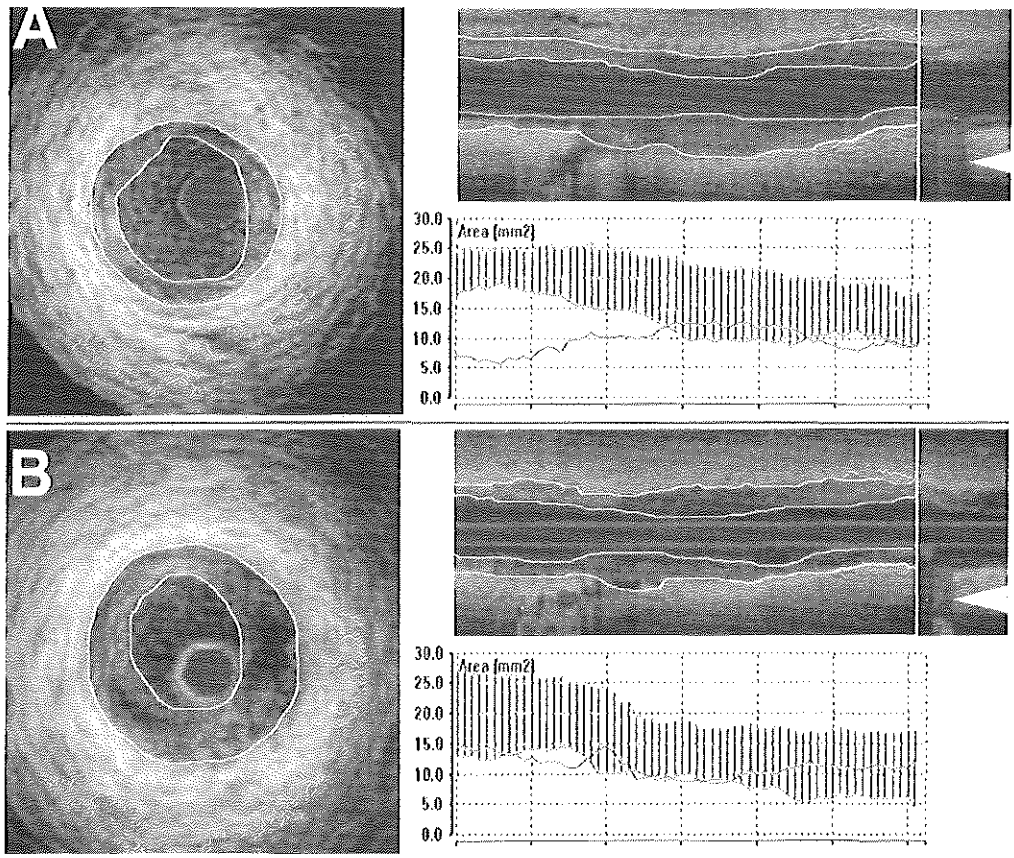

Figure 2. *(A) Post-procedure 3-D IVUS imaging and volumetric quantification. Left panel: one planar cross-section view is displayed and the lumen (inner line) and EEM (outer line) area are delineated. Top right panel: one longitudinal view is displayed with the anatomical landmark (side branch = arrowhead) used to determine the segment for volumetric quantification. Lumen and EEM boundaries are delineated in the segment of interest. Bottom right panel: a graphic displays the consecutive areas of the entire set of planar images — used for volumetric quantification. The values of the plaque area are shown as a gray field between two lines (vessel and lumen areas). The absolute value of the plaque area can be derived from this field, but is also displayed as single black line. (B) 3-D IVUS imaging and volumetric quantification at follow-up. The correct match is determined on longitudinal and planar views using the anatomical landmark (arrowhead). Lumen and vessel boundaries are delineated in both planar and longitudinal views. The graphic of the vessel, lumen and plaque areas is also displayed.*

Thus, the results of this study consisted of a cohort of 21 patients with successful post-procedure and 6-month 3-D IVUS assessment. Sixteen patients were actually treated with radioactive source, while 5 patients received placebo treatment. In the radiation group, 6 patients received 28 Gy, 5 patients received 35 Gy and 5 patients received 42 Gy. An additional stent was implanted after BA in 7 patients (44%) in the irradiated group and 3 patients (60%) in the placebo group (p = NS). All patients were discharged on day 2 after the procedure without complication. The medication at discharge consisted of aspirin (250 mg/day) and ticlopidine (250 mg/day, only for stented patients). The dwell time for delivering the prescribed radiation dose ranged from 1.5–8.0 minutes. There was no complication related to the radiation treatment protocol. Clinical and demographic characteristics were similar between placebo and irradiated patients (Table 1). Post-procedure and follow-up IVUS measurements are summarized in Table 2. At 6-month follow-up, we observed a smaller minimal lumen area (MLA) and greater percentage of plaque area in the placebo group compared to irradiated group.

Table 1. Baseline and demographic characteristics

Variable	Irradiated (n = 16)	Placebo (n = 5)	p-value
Age (years)	59.2 (9.6	56 (10.9	NS
Gender (male)	11 (79%)	4 (80%)	NS
Diabetes	0	0	NS
Smoking	6 (38%)	2 (40%)	NS
Hypercholesterolemia	9 (56%)	3 (60%)	NS
Hypertension	5 (31%)	0	NS
Family History of coronary artery disease	6 (38%)	2 (40%)	NS
Previous myocardial infarction	7 (44%)	3 (60%)	NS
Canadian Cardiovascular Society angina status, 3/4	12 (75%)	5 (100%)	NS
Treatment site at left anterior descending artery	7 (34%)	3(60%)	NS
Restenotic lesion	4 (25%)	1 (20%)	NS

NS = not significant

Table 2. Post-procedure and follow-up 3-dimensional intravascular ultrasound measurements.

	TVV (mm^3)		PV (mm^3)		LV (mm^3)		MLA (mm^2)		Plaque burden at MLA (%)	
	Post	FU	Post	FU	Post	FU	Post	FU	Post	FU
Irradiated (n = 16)	385 ± 110	403 ± 133	198 ± 63	214 ± 74	185 ± 60	190 ± 63	4.8 ± 1.6	4.7 ± 1.3	63 ± 9	64 ± 9
Placebo (n = 5)	415 ± 101	391 ± 98	210 ± 58	228 ± 69	205 ± 62	163 ± 44	4.7 ± 1.2	3.3 ± 1.3	60 ± 16	76 ± 14
p-value	NS	NS	NS	NS	NS	NS	NS	0.046	NS	0.042

TVV = total vessel volume; PV = plaque volume; LV = lumen volume; MLA = mean lumen area; post = post-procedural; FU = follow-up

Volumetric changes (Δ) after 6 months: Placebo versus irradiated. As illustrated in Figure 3, the volumetric change of the total vessel volume (ΔTVV) occurred in an opposite direction between irradiated and placebo patients. While the irradiated patients demonstrated a positive ΔTVV (increase of the TVV at follow-up), placebo patients demonstrated a negative ΔTVV (decrease of the TVV at follow-up). Equally, an opposite behavior was observed regarding the volumetric changes of the lumen volume (ΔLV). The placebo group demonstrated a negative ΔLV, whereas irradiated patients showed a positive ΔLV ($p = 0.01$). However, plaque volume (ΔPV) increased in both groups in a similar degree (positive ΔPV). There was no relationship between prescribed doses and volumetric changes.

Irradiated patients: Stent versus balloon angioplasty. In the analysis of the entire (27 mm) irradiated segment, stented patients (n = 7) demonstrated similar volumetric changes after 6 months compared to BA patients (n = 9), as illustrated in Figure 4. It is of interest to note that in the stented patients, PV consists of the total amount of plaque outside and inside the stent. In addition, this analysis quantified the entire irradiated segment including segments covered and uncovered by stents.

Analysis of the stented segment (irradiated patients). In this analysis, only the segments covered by stent were selected for volumetric quantification. The average stent length (segment analyzed) was 18.1 ± 6.36 mm. Post-balloon dilation was performed in all cases at a mean pressure of 14.6 ± 3.2 atm. At follow-up, we observed a neointimal hyperplasia volume of 1.89 ± 2.99 mm^3 with a mean percentage neointimal formation of 1.47 ± 2.49%. The TVV within the stented segment demonstrated a non-significant increase after 6 months (post-procedure TVV of 260 ± 68 mm^3 versus 272.2 ± 97 mm^3 at follow-up; p = NS). The plaque volume outside the stent also demonstrated a non-significant change at follow-up (post-procedure PV of 131 ± 32 mm^3 versus 141 ± 63 mm^3 at follow-up; p = NS). Stent volume remained unchanged (no recoil) after 6 months (129.5 ± 39 mm^3 post-procedure versus 131 ± 39 mm^3 at follow-up; p = NS).

DISCUSSION

This pilot investigation demonstrates that beta radiation affects vessel remodeling after percutaneous intervention. In addition, neointimal formation within the stented segment was almost absent in our irradiated population. However, the small size of our stented

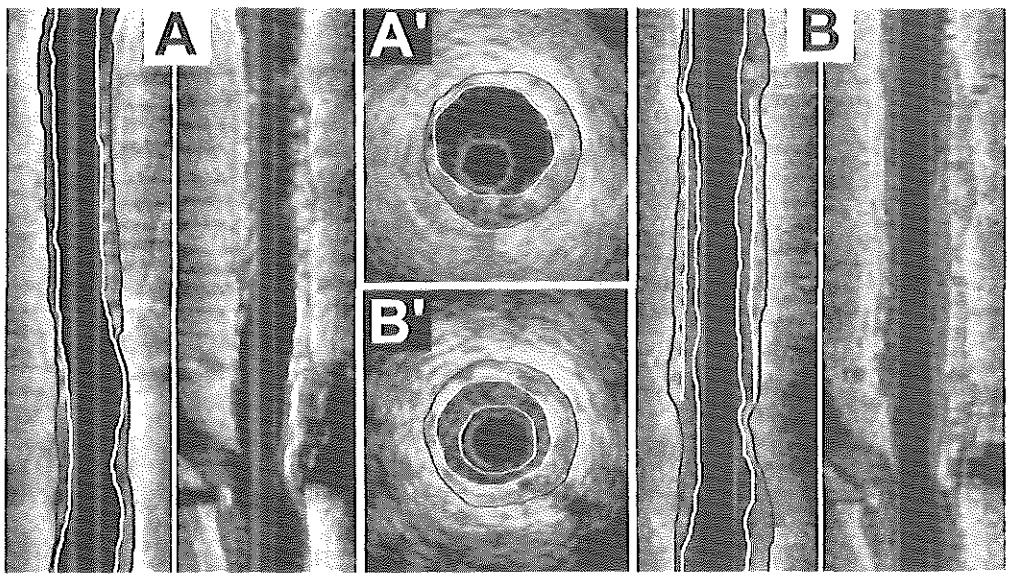

Figure 3. *Three-dimensional intravascular ultrasound analysis of stented coronary segments. Post-procedure longitudinal (A) and planar (A') views, as well as follow-up longitudinal (B) and planar (B') views are displayed. Lumen and stent (white lines), and vessel boundaries (black line) are delineated in the planar image and in one of the longitudinal views. At follow-up (B, B'), we can observe the delineation of neointimal hyperplasia between the lumen and stent boundaries (white lines). The visualization of the EEM boundary behind the stent and neointimal hyperplasia are illustrated in the longitudinal views without contours as well as the anatomical landmark (side branch with a spot of calcium in the ostium) used for correct match between post-procedure and follow-up analyses.*

population should be taken into account before drawing any definitive conclusions.

Considering that vessel shrinkage accounts for about 50–70% of the mechanism of restenosis after conventional BA[3] and radiation has been shown to reduce the restenosis rate in the setting of BA,[10] the conclusion that radiation affects vessel remodeling seems logical. Clinical[13] and experimental data[14,15] have already suggested the influence of radiation on vessel remodeling.

IVUS analysis of patients enrolled in the BERT trial has also suggested that radiation may prevent vessel shrinkage after BA.[11,12] The use of single cross-section planar IVUS images limited the study of Meerkin et al. assessing the influence of radiation on vessel remodeling. The four coronary aneurysms reported by Condado et al. exemplified the extreme expression of this phenomenon in a series of patients receiving high doses of gamma radiation.[23]

In accordance to the findings of the present study, a recent clinical investigation from our group using the same methodology has demonstrated that beta radiation using a $^{90}Sr/Y$ source influences vessel wall remodeling after BA.[13] In 21 patients analyzed, there was a significant increase of the total vessel volume after 6 months in patients enrolled in the BERT 1.5 trial.[13] However, the exclusion of stented patients in this previous study did not allow further insight into the mechanism of radiation on the inhibition of neointimal proliferation.

The opposite pattern of change in total vessel volume between the irradiated population (positive ΔTVV) and placebo (negative ΔTVV) observed in our study may confirm the influence of radiation on vessel wall remodeling. In addition, the combination of a smaller total vessel volume and bigger plaque volume at follow-up accounted for the reduction of lumen observed only in the placebo group. Similar patterns of structural vessel changes have been previously reported after conventional percutaneous intervention in non-irradiated coronary segments.[3]

On the other hand, gamma radiation has been shown to decrease the incidence of restenosis in stented patients treated for in-stent restenosis.[8,9] Once again, another logical conclusion may rise in favor of radiation inhibiting neointimal formation. Clinical and experimental reports have emphasized the effect of gamma radiation on inhibiting neointimal formation.[5–9]

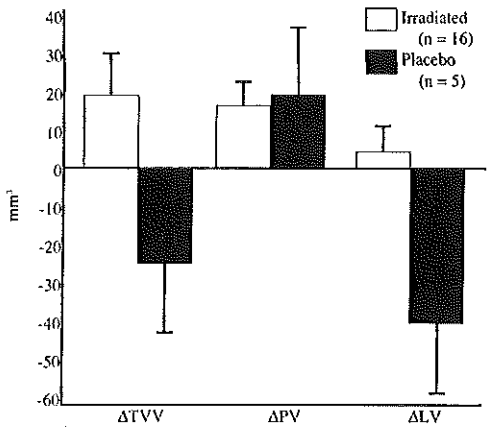

Figure 4. *Volumetric Changes (Δ) of the total vessel (TVV), plaque (PV), and lumen (LV) in the target (27 mm long) coronary segments after 6 months. Comparison between irradiated and placebo patients. p = 0.065 for ΔTVV; p = 0.01 for ΔLV.*

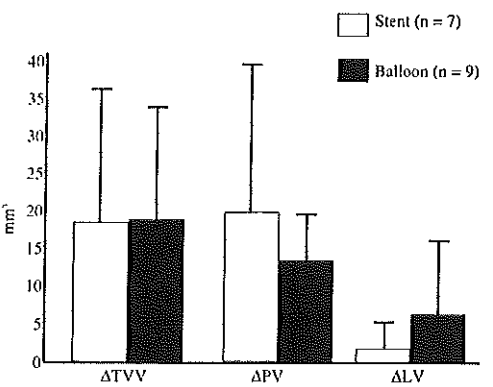

Figure 5. *Volumetric Changes (Δ) of the total vessel (TVV), plaque (PV), and lumen (LV) within the irradiated coronary segment (27 mm long) after 6 months. Comparison between balloon angioplasty and stent patients. p = NS for ΔTVV, ΔPV, and ΔLV.*

In our stented population, the amount of neointimal formation was only 1.89 mm³, which suggests that beta radiation also inhibits neointimal formation after conventional stenting.

The assessment of plaque growth outside the stent is a novelty in the setting of brachytherapy. A previous IVUS study has demonstrated the progression of plaque mass within and surrounding conventional stents.[25] However, a recent report investigating 15 non-irradiated stented coronary segments did not demonstrate plaque growth outside the stent.[23] In our study, the plaque volume outside the stent and TVV showed a non-significant increase of 10 and 12 mm³ after 6 months, respectively. Further IVUS studies should investigate the influence of radiation on neointimal formation, plaque growth (outside the stent), as well as vessel remodeling in stented patients.

This pilot study contributes to a better understanding of the complex interaction between radiation and vascular structures. By comparing for the first time three-dimensional IVUS parameters of beta-irradiated and non-irradiated coronary segments, our study demonstrates that radiation affects vessel remodeling after percutaneous intervention. In addition, this seminal study suggests that beta radiation may also inhibit neointimal formation after stenting. It is nevertheless of interest to note that to date only a few reports are available using serial IVUS investigation after either beta radiation in the setting of BA or gamma radiation in the setting of stenting. Thus, the confirmation of these findings by a large population study with volumetric IVUS assessment is required.

Study limitations. The size of the population is the major limitation of this pilot study, which has insufficient statistic power to demonstrate some differences. However, this is a pioneering investigation using 3-dimensional intravascular ultrasound to assess the effects of beta-radiation after either balloon angioplasty or stenting. In addition, this is the first study to compare irradiated versus non-irradiated coronary segments by means of a volumetric assessment in a randomized fashion. The similarity between our findings and those previously reported on either irradiated[23] or non-irradiated coronary segments[3] may endorse our conclusions.

The difficulty to assess patients with severe restenotic lesions is a limitation of the methodology used in this study. Thus, the assessment of the mechanism involved in an "aggressive" vessel wall reaction after intervention, as observed in one patient of this study, cannot be performed.

Although the prescribed dose was not related to any vessel structural change after 6 months, the actual dose received by the target segments was not calculated in this study, limiting any dosimetric consideration.

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CHAPTER 9

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

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Abstract

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 this study was to assess the "edge effect" in non-injured margins adjacent to the irradiated segments after intracoronary catheter-based β-irradiation. **Methods and Results:** Fifty-three vessels were assessed by means of three-dimensional intravascular ultrasound at post-procedure and 6-8 months follow-up. Fourteen vessels (placebo group) did not receive radiation (sham source), whereas 39 were actually irradiated. In the irradiated group, 48 edges (5-mm in length) were identified as non-injured, whereas 18 non-injured edges were selected in the placebo group. We compared the volumetric IVUS measurements of the non-injured edges of the irradiated vessels with the fully irradiated non-stented segments (IRS, n=27) (26-mm segments receiving the prescribed 100% isodose) and the non-injured edges of the placebo patients. The lumen decreased (6-mm^3) in the non-injured edges of the irradiated vessels at follow-up (p=0.001). We observed a similar increase in plaque volume in all segments: non-injured edges of the irradiated group (19.6%), non-injured edges of the placebo group (21.5%) and IRS (21.0%). Total vessel volume (TVV) increased in the IRS between 3 groups. No edge segment was subject to repeat revascularization. **Conclusions:** The edge effect occurs in the non-injured 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 non-measurable device injury may be considered as a plausible alternative explanation.

Introduction

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 (i.e. stent implantation)[1,2], it has become an important issue after the introduction of intracoronary brachytherapy in the clinical practice.

Recently, the edge effect has been reported in patients receiving 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 at the stent margins was demonstrated[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 three-dimensional (3-D) volumetric intravascular ultrasound (IVUS) investigation, our group has 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 three reports, the authors have 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].

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

Methods

Study Population

From April/97 to March/99, 56 *de novo* lesions of 50 patients were 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 stents overlapping outside the irradiated area. In addition, 3D-IVUS analysis was not carried out either at post-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 thrombotic occlusion, and 2 other patients without recurrent angina refused follow-up angiogram. The placebo group consists of 14 patients successfully treated with conventional balloon angioplasty or single stent implantation during the same period. In these patients, the radiation delivery catheter was also introduced in 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 non-irradiated 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 ischemic-related symptoms or positive stress testing. Those with myocardial infarction within 72 hours before the treatment or left ventricular ejection fraction < 30% were not included in this study. Angiographic inclusion criteria consists 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 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, which contain pure ß-emitting $^{90}Sr/^{90}Y$, and is bordered by 2 gold markers (30-mm in length). The longitudinal distance of "full" prescribed dose (100% isodose) coverage measured by radiochromic films is approximately 26 mm (Novoste Corp, data on file, personal communication). The profile of the catheter is 5 French and the source train is not centered.

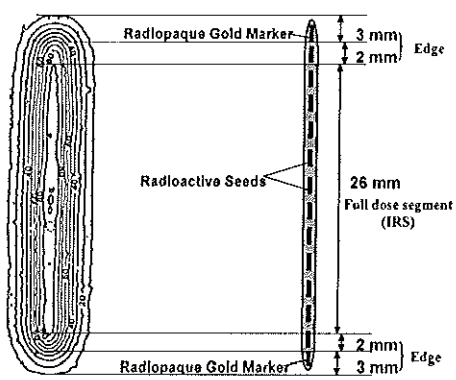

Figure 1. Isodose rate contour map and radiation source train
Left side: Isodose rate contour map at a depth of 1.89 mm (10 mGy/s contour intervals) as described by NIST (The National Institute of Standards and Technology). This depth (1.89 mm) illustrates an isodose model to resemble the radius of the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

Procedure

All patients received aspirin (250 mg/day) and heparin IV (10.000 IU) before the procedure, whereas stented patients also received ticlopidine (250 mg/day) for 30 days. Heparin was given to maintain the activated clotting time >300 sec. 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 motorized pullback were carried out. If stenting was indicated due to a residual stenosis > 30% diameter stenosis or dissection, a stent was implanted with high-pressure post-dilatation and IVUS guidance. Finally, repeat angiography and IVUS were carried out. Intracoronary nitrates were administered immediately prior to each of the IVUS pullbacks. At follow-up (6-8 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 3D-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 Corporation, Maple Grove, MN). ECG-gated 3-D IVUS image acquisition and digitization was performed by a computerized workstation (EchoScan, Tomtec, Munich, Germany)[10]. IVUS images were acquired coinciding 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/step by 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 corresponding to the lumen, media and/or stent boundaries. Volumetric data were automatically calculated by the formula: $V= \Sigma^{n}_{i=1} A_i \times H$, where V = volume, A = area of external elastic membrane (EEM), lumen, stent or plaque in a given cross-sectional ultrasound image, H = slice thickness of the cross section (0.2mm), and n = the number of digitized cross-sectional images encompassing the volume to be measured[11]. Off-line analyses were performed by three independent experienced analysts (KK, MC, MS), who checked and edited all the contours of the planar images. The accuracy of this method has been validated in vitro (phantom) and in vivo[12]. Intra- and inter-observer variability of this system has also been determined in clinical protocols[9]. 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 volume, -0.3 ± 1.0% in plaque volume using 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 the delivery catheter and the relation between anatomic landmarks and the two radiopaque markers of the radiation source were noted. Typically, the aorto-ostial junction, side branches and/or stent were used as landmarks. During the subsequent IVUS imaging pullback, this reference point was recognized and used for selecting 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 to that post-procedure. The longitudinal distance of the 100% isodose is approximately 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 part of the radiation source train, and the edges of the IRS as the adjacent (distal and proximal) 5-mm coronary segments, which consisted of the 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 since ß-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 less than 1 Gy at 5 mm.

In order to select the non-injured 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 cineframe of angiograms which 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 off-line analysis, using the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands). 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 part of the radioactive source train). Thereby all the injured edge segments were excluded. At follow-up, it was also possible to determine the non-injured edge segments by the same method, since all the follow-up cinefilms were taken in the same views as pre- and post-procedure. This angiographic analysis was performed independently by 2 cardiologists (KK, MC). Only the edges, which both investigators regarded as non-injured segments were finally considered as non-injured edges. There was only 10 % disagreement in the definition of injured irradiated edge segment using this methodology. The 3-mm stent edges were also considered as injured segments since the balloon of the stent delivery system may protrude about 2-3 mm outside the stent.

Quantitative 3-D IVUS Analysis

Total vessel volume (TVV) determined by EEM boundaries and lumen volume (LV) were measured. Plaque volume (PV) was automatically calculated by subtracting LV from TVV. 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, which affects volume calculations, percent delta change (delta volume / post-procedure volume) was also calculated.

Remodeling was defined as a continuous process involving 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 to post-procedure measurements by at least two standard deviations (± 1.3%) of the intra-observer variability. By using this technique, the potential intrinsic error of the method may be avoided[16,17].

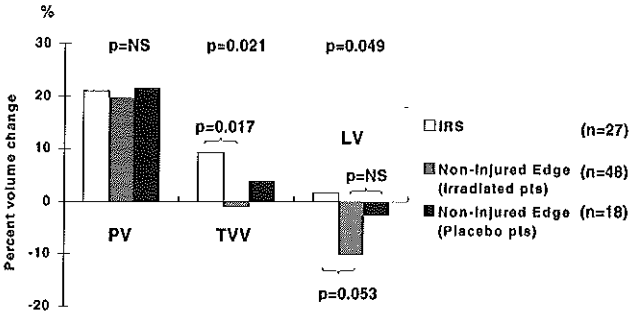

Figure 2. Comparisons of the percent volume changes among IRS and the non-injured edges of both irradiated and placebo patients.
PV = plaque volume, TVV = total vessel volume, LV = lumen volume,
IRS = fully irradiated segments, pts = patients

Statistical analysis

Quantitative data are presented as mean ± standard deviation. Comparisons between post-procedure and follow-up IVUS parameters were compared by means of paired student's t test. Comparisons of the IVUS data among 3 groups (non-injured edge of the irradiated vessels, IRS, and non-injured edge of the placebo group) were performed using one-way analysis of variance (ANOVA) test. Bonferroni test was applied for comparison between each groups. The difference between proximal and distal edge was compared by two-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 Correlation. A value of $p<0.05$ was considered statistically significant.

Table 1. Clinical and Lesion characteristics.

	Irradiated (n=36)	Placebo (n=14)	p value
Age, y	57±9	57±9	NS
Male, n (%)	27 (75)	3 (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, (%)	13 (36)	5 (36)	NS
Multivessel disease, (%)	12 (33)	1 (7)	NS
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

PTCA = percutaneous transluminal coronary angioplasty, LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, RCA = right coronary artery

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 6-8 months follow-up. Target lesion revascularization was performed after follow-up angiogram in 6 vessels in the irradiated group (16%) and 2 vessels in placebo group (14%). The non-injured edges were not involved in any of the restenotic lesions that required further intervention in both groups.

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

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

Table 2. Volumetric measurement of 3-D IVUS

	IRS (n=27)		**Non-Injured Edge Irradiated vessel** (n=48)		**Non-Injured 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

* $p < 0.001$, † $p = 0.06$, ‡ $p = 0.004$, § $p = 0.001$, IRS = irradiated segment with full-dose, Post = post-procedure, PV = plaque volume, TVV = total vessel volume, LV = lumen volume

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 non-injured edges in the post-procedure IVUS analysis but no edge (radiation or placebo group) had more than 50% plaque burden. Compared to post-procedure measurement, there was a significant increase in PV in the non-injured edges of the irradiated vessels ($\Delta PV = 4$ mm^3) at follow-up. Since TVV on average decreased by -2 mm^3 (p = NS), LV decreased at follow-up in the non-injured edge of the irradiated vessels ($\Delta LV = -6$ mm^3). In the placebo group, there was also a tendency of plaque increase at follow-up ($\Delta PV = 4$ mm^3) in the non-injured edge of the placebo group ($p = 0.06$).

Comparisons among the geometric changes of 3 groups (IRS, non-injured edges of the irradiated vessels and non-injured edges of the placebo group) are demonstrated in Figure 2. The percent increase in PV was similar among IRS, non-injured edges of the irradiated vessels and those of placebo group (+21.0% vs. +19.6% vs. +21.5%, respectively). TVV increased in IRS significantly between 3 groups (+9.4% at IRS; –1.0% at non-injured edges of the irradiated vessels; +3.8% at non-injured edge of the placebo, p=0.021). The difference was observed only between IRS and

non-injured edges of the irradiated vessels by post-hoc test (p=0.017). Percent changes in LV were different (+1.7% vs. -10.0% vs. –2.5%, respectively, p=0.049) among 3 groups. LV tended to decrease in non-injured edges of irradiated patients compared with IRS (p=0.053).

Comparisons between the geometric changes of the proximal and distal non-injured 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 compared to the distal edges (+27.0% vs. +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).

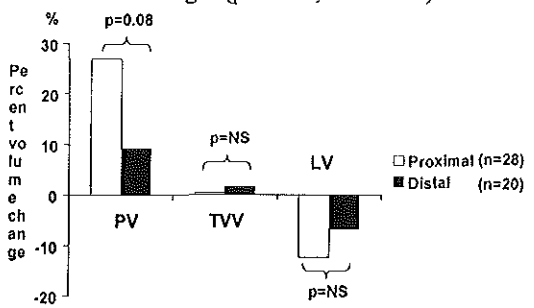

Figure 3.
Comparisons of the percent volume changes between proximal and distal edges in the irradiated vessels.
PV = plaque volume, TVV = total vessel volume, LV = lumen volume

Discussion

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

Lumen loss was observed in the non-injured edges of the irradiated group. The decrease in LV observed in these edges was mainly due to the lack of positive vessel remodeling (i.e. no remodeling)[15] to accommodate the plaque increase, which occurred similarly in all analyzed segments. Likewise, lumen also decreased (2.5%) in the non-injured 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 non-irradiated 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 non-injured edges compared to placebo. Plausible explanations for the PV increase in the non-injured edges of both irradiated and placebo groups would be the non-measurable vessel injuries; guiding catheter (i.e. deep engagement) during the procedure or the devices when crossing coronary segment (guide-wires, 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 5-French 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 less aggressive approach: avoidance of deep catheter engagement, guide wire 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.

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

In conclusion, the edge effect occurs in the margins of catheter-based β-radiation 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 in the cause of the edge effect, and clinically not-assessable device injury would rather be considered as a plausible explanation for this phenomenon. Clinically, the "edge effect" observed in our mid-term follow-up IVUS study did not represent a drawback of the catheter-based intracoronary β-radiation.

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, since a smaller number of patients are necessary to demonstrate statistical differences in studies using volumetric IVUS parameters[21].

Minor inaccuracy in the selection of the segments of interest cannot be completely ruled out, although the methodology applied in our study was the most appropriate at this time. Ideally, intervention devices incorporating 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 (i.e. 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, our study was not aimed at establishing a threshold of dose to be delivered to the irradiated target site, since an adjacent coronary segment will invariably receive low-dose of radiation.

The 6-8 months 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]. Then, one question still remains to be elucidated: Does endovascular radiation have any influence on the progression of atherosclerosis, especially in the adjacent non-target irradiated segments?

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CHAPTER 10

Positive Geometric Vascular Remodeling is seen after Catheter–Based Radiation Followed By Conventional Stent Implantation, But Not After Radioactive Stent Implantation

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Abstract

Background: Recent reports have shown that intracoronary radiation affects not only neointimal formation but also vascular remodeling. Given the different way in which radioactive stents and catheter–based techniques deliver beta-radiation one may expect different patterns of remodeling after each technique.

Method and Results: We analyzed remodeling in 18 patients after conventional stent implantation (C), 16 patients after low activity (LA) radioactive stent implantation, 16 patients after higher activity radioactive stent implantation (HA) and finally 16 patients who underwent catheter–based beta-radiation followed by conventional stent implantation (CBS). Intravascular ultrasound with 3 – dimensional reconstruction was used post stent implantation and at 6 – month follow – up to assess remodeling at the stent edges and within the margins of the stent. Baseline, vessel and procedural characteristics were similar between groups. In – stent neointimal hyperplasia was inhibited by HA (neo-intimal volume = 9.0mm^3) and by CBS (neo-intimal volume = 6.9mm$^{3)}$ compared with LA (neo-intimal volume = 21.2mm^3) and C (neo-intimal volume = 20.8mm^3), p=0.008. No difference in plaque or total vessel volumes was seen behind the stent in the C, LA or HA groups. However a significant increase in plaque behind the stent (+15%) and TVV (+8%) was seen in the CBS group. At the stent edges, no edge restenosis was witnessed in the C, LA or CBS groups. Edge restenosis was seen after HA implantation and appeared to be due mainly to an increase in plaque and to a lesser degree to negative remodeling.

Conclusions: Distinct differences in the patterns of remodeling exist between conventional, radioactive and catheter–based radiotherapy with stenting. Users of radiation need to be alerted to the deleterious remodeling seen at the stent edges after higher – dose radioactive stent implantation and behind the stent after catheter–based radiation and stenting.

Introduction

In our enthusiasm to control vessel recoil and remodeling after balloon angioplasty (BA), stent implantation has become increasingly popular. With conventional stenting we have eliminated recoil and remodeling as components of the restenotic process. However this has been at the cost of exacerbating neo intimal proliferation secondary to chronic vessel wall irritation, leading to in-stent restenosis[1,2].

Intracoronary radiation has been developed in an attempt to decrease restenosis after BA and stent implantation. Two parallel technologies, one employing radioactive stents[3-7], the other catheter – based radiation[8-10], have been the subject of both animal and human studies. Given the different dose rates and total doses delivered by each method, intuitively one may expect different patterns of remodeling subsequent to each approach.

Whereas the effect of catheter-based radiation after BA on vascular remodeling has been described [11], the response of the arterial wall to catheter-based radiation and subsequent stent implantation is not described. Preliminary studies have reported the effect at the stent edge after radioactive stent implantation[4]. These reports did not encompass the response behind the stent in the arterial wall however.

The aim of this study was to describe the response of the coronary artery to radiation and stenting, by looking at the stent and its edges after radioactive stent implantation and also after catheter – based radiation with stent implantation.

Methods

Patient Selection

We analyzed geometric vascular remodeling in 4 groups of patients:

- those who had undergone implantation of ^{32}P radioactive stents at activity levels of 0.75-1.5μCi (Isostent™ Inc., San Carlos, CA, USA).
- those who had undergone implantation of ^{32}P radioactive stents at activity levels of 6.0-12μCi (Isostent™ Inc., San Carlos, CA, USA).
- those who had undergone conventional stent implantation after suboptimal BA (clinically significant dissection or residual stenosis > 30%) and catheter–based radiation.
- those who had undergone conventional stent implantation after suboptimal BA.

Stents analyzed were from patients with single native vessel coronary artery disease, normal left ventricular function and objective evidence of ischemia. All groups were matched for patient baseline characteristics, vessel size, lesion and stent length. Stents placed in the ostial position or adjacent to major side – branches, such that the stent edges were unable to be analyzed, were excluded from analysis. Only patients who had completed 6 – month angiographic and IVUS follow – up were included.

Implantation technique

The same group of cardiologists, using a similar technique implanted all stents.
Predilation of the lesion was performed, followed by stent implantation using either a pre - mounted stent or the Johnson & Johnson Intervention Systems delivery system (Johnson & Johnson Interventional Systems Co, Warren NJ, USA). Higher – pressure balloon inflation to ensure good strut apposition to the vessel wall was then peformed. At this time we used a shorter balloon to ensure that the edges of the balloon did not extend beyond the limits of the stent. Intravascular ultrasound was used to ensure optimal stent deployment.

Medication

Patients received 250 mg aspirin and 10000 international units heparin at the initiation of the procedure and the activated clotting time was maintained at > 300 seconds. All patients received aspirin 80mg daily indefinitely and ticlopidine 250 mg BID for 2 weeks (C) or clopidogrel 75mg daily for 12 weeks (LA, HA and CBS), after stent implantation.

Radioactive stents

The BX™ stent (Isostent™ Inc., San Carlos, CA, USA) was the only radioactive stent implanted in this trial. It was 15mm in length and available in diameters of 3.0 & 3.5 mm. The BX™ stent was made radioactive by Phosphorus-32 (^{32}P). The initial activity of the stents was measured and thereafter it was calculated at what date the activity had decreased to 0.75-1.5 μCi or 6-12 μCi, suitable for implantation. The dose delivered over 100 days at 1 mm from the stent surface was calculated for each implanted stent.

Catheter–based radiation system

The Beta-Cath System (Novoste Corp., Norcross, GA) was used to deliver β-radiation ($^{90}Sr/^{90}Y$) at the site of coronary intervention. Dose was prescribed precribed at 2mm depth from the center of the source. The device consisted of 3 components: (1) the transfer device which stored the radiation source train and allowed the positioning of these sources within the catheter; (2) the delivery catheter, which was a 5 French (F) multilumen over-the-wire non-centered catheter which used saline solution to send and return the radiation source train; and (3), the radiation source train which consisted of a series of twelve independent cylindrical seeds which contained the radioisotope ^{90}Sr sources and was bordered by 2 gold radiopaque markers separated by 30 mm. Other device and procedural details have been previously published by this group.[11]

Definitions

Stent Edges: Stent Edges were defined as those volumes axially 5mm proximal and distal to the final stent strut. An edge restenosis was defined as an angiographic restenosis > 50% at 6-month follow–up located at either stent edge. An edge - effect was defined as any stent-edge renarrowing.

Patients with balloon – injured edges that failed to receive radiation in the catheter – based radiation group were excluded. In other words no stents implanted in areas of geographical miss were included in this study.

IVUS image acquisition analysis

After the final balloon inflation and administration of intracoronary nitrates, ECG-gated IVUS pullback was performed. This was repeated at 6 month follow-up. The segment subject to 3-D reconstruction was examined with a mechanical IVUS system (ClearView, CardioVascular Imaging System, CVIS, Sunnyvale, CA) with a sheath-based IVUS catheter incorporating a 30 MHz single-element transducer rotating at 1800 rpm. The IVUS transducer was withdrawn through the stationary imaging sheath by an ECG-triggered pullback device with a stepping motor.[12] IVUS images were aquired coinciding with the peak of the R wave, which eliminates the artefacts caused by the movement of the heart during the cardiac cycle. After each image acquisition the transducer was withdrawn 0.2mm to aquire the next image coincident with the R – wave. The ECG-gated image acquisition and digitation was performed by a workstation designed for the 3-D reconstruction of echocardiographic images [12] (EchoScan, Tomtec, Munich, Germany). A Microsoft Windows™-based contour detection program, developed at the Thoraxcenter, Rotterdam was used for the automated 3-D analysis of up to 200 IVUS images.[13] This program constructs two longitudinal sections and identifies the contours corresponding to the lumen-intima and media-adventitia boundaries using a minimum-cost based software algorithm. The feasibility, reproducibility and the inter- and intraobserver variability of this system have been previously validated in clinical protocols[11].

Quantitative IVUS analysis

At the stent edges the area encompassed by the lumen-intima and media-adventitia boundaries defined the luminal and the total vessel volumes, respectively. The difference between luminal and total vessel volumes defined the plaque volume. Within the boundaries of the stent total vessel volume

volume (TVV), stent volume, neointimal hyperplasia (NIH), plaque behind the stent (PBS= TVV – stent volume) and lumen volumes were obtained.

The assessment of TVV or EEM in stented patients has previously been reported[14]. Although, in this previous report the delineation of TVV/EEM was not possible in some patients due to stent shadowing, in our study the delineation of EEM boundary was possible in all stented patients. When the TVV/EEM boundary was not visible in a single cross – sectional view, the computer extrapolated it from the contours of the immediately previous and following cross – sections. In addition the use of 3 – dimensional reconstruction with multiple longitudinal views facilitates the visualization of vessel structures outside the stent.

Table 1. Clinical Characteristics

	Conventional	LA	HA	CBS
Patient No	18	16	15	17
Age (mean)	58 (42-76)	60 (43-74)	59 (42-75)	57 (45-74)
Male (%)	70	66	70	60
Prior MI (%)	40	40	45	40
Unstable angina (%)	60	50	65	55
Smoking (%)	40	55	40	40
Hypercholestrolemia (%)	60	62	65	55
Family history (%)	33	42	30	40
Hypertension (%)	40	42	30	33
Diabetes (%)	5	5	10	6

Statistical analysis

Quantitative data are presented as mean ± standard deviation. Volumetric data derived from the 3-D reconstruction of the IVUS imaging were compared immediately after treatment and at follow-up using the two-tailed paired Student's t-test. Comparison between groups was performed using one – way analysis of variance (ANOVA). A value of $p<0.05$ was considered statistically significant.

The Medical Ethical Committee of the University Hospital Rotterdam approved the study and all patients provided written informed consent before the procedure.

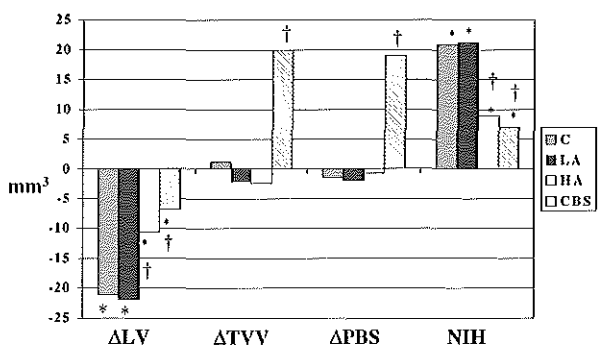

Figure 1.
Remodeling within the margins of the stent.
* = $p < 0.05$; post vs follow-up, † = $p < 0.05$ between groups.

Results

Baseline Characteristics

Eighteen patients were enrolled in the conventional group (C), 16 patients in both the 0.75-1.5μCi (LA) and 6.0-12μCi (HA) radioactive stent groups and finally 17 in the group employing catheter – based radiation plus a stent (CBS). In the conventional group 10 Multilink and 8 NIR stents were implanted. Baseline characteristics are similar between all groups and are described in Table I. Lesion and procedural characteristics are described in Table 2. No statistically significant differences were seen between groups in the parameters described in Table 2. A comparison of volumetric data measured at the stent edges and within the margins of the stent is presented in Tables 3 and 4.

Table 2 Procedural characteristics

	C	LA	HA	CBS
Vessel				
LAD	10	9	9	9
LCx	4	3	4	4
RCA	4	4	3	4
Lesion length (mm)	9.6 ± 3.3	12.1 ± 3.8	10.1 ± 3.3	11.9 ± 4
Stent length (mm)	14.6 ± 3.8	15.0	15.0	15.2 ± 4.1
Balloon length-post	14.8 ± 3.4	14.4 ± 2.8	14.1 ± 2.6	15.1 ± 3.6
Final balloon size (mm)	3.2 ± 0.4	3.1 ± 0.6	3.4 ± 0.5	3.2 ± 0.5
Max inflation pressure[1]	11.5 ± 2.4	11.6 ± 2.6	10.2 ± 2.8	12.2 ± 2.6
Max inflation pressure[2]	14.6 ± 3.2	15.2 ± 2.4	15.8 ± 1.7	15.4 ± 3.3
Balloon-to-artery ratio	1.04 ± 0.05	1.12 ± 0.06	1.10 ± 0.06	1.12 ± 0.05

Max inflation pressure[1] = balloon at time of stent implantation
Max inflation pressure[2] = balloon inflation within stent

In stent inhibition of NIH

Intra - stent NIH was decreased after higher - activity radioactive stent implantation and CBS (p=0.008, ANOVA). Lower activity radioactive stents had an effect similar to that of conventional stent implantation (see Table 4 and Figure 1).

Behind stent

Conventional stents and both low and higher activity radioactive stents demonstrated an absence of remodeling behind the stent, with no significant changes in TVV or plaque volumes. This is in contrast to the CBS group which demonstrated a significant increase in plaque (post Vs follow-up: + 15%, p=0.002) and an increase in TVV (post Vs follow-up: + 8%, p=0.003). Inter-group comparison showed that this change was significant, (Table 4, p = 0.01). Further comparisons of changes within and between groups are demonstrated in figure I. No chronic recoil of the stent was seen in any group.

Table 3. Mean (SD) volumes for the edge proximal and distal to the stent (10mm length)

Edge (mm^3)	LV post	LV F/UP	TVV Post	TVV F/UP	Plaque Post	Plaque F/UP
C	67.7 (18.9)	58.3 (19.3)*	124.4 (32.6)	116.5 (34.1)*	56.7 (22.6)	58.2 (23.1)
LD	75.2 (39.0)	67.3 (34.4)*	126.6 (58.0)	116.4 (49.0)*	51.4 (24.5)	49.1 (21.0)
HD	74.9 (23.0)	63.0 (23.7)*	126.2 (44.9)	117.6 (46.2)*	51.3 (16.4)	54.6 (16.1)
CBS	72.6 (27.7)	61.1 (26.3)*	133.2 (48.5)	138.9 (46.5)†	60.6 (26.1)	77.8 (28.6)*†

* = $p < 0.05$ Post vs Follow-up (F/UP). † = $p < 0.05$ between groups (ANOVA).

Stent edge

No significant difference between groups was seen at baseline (post stent implantation). All groups demonstrated late lumen loss at the stent edge. At the stent edges remodeling is similar after both conventional and low – activity radioactive stent implantation. In these groups there is evidence of a decrease in TVV, with little change in plaque as a cause of late lumen loss (Figure 2). At higher activity levels of radioactive stent the presence of stent edge restenosis becomes apparent. In the ^{32}P group a target segment restenosis (angiographically > 50%) was observed in 7 patients at the stent edges. This was more common at the proximal edge (6/7). The major mechanism of such restenosis appears to be due to an increase in plaque at the stent edge. In non - restenotic patients the edge effect appears due to a decrease in TVV and to a lesser degree, an increase in plaque (Figure 3).

After CBS the edge effect is largely due to an increase in plaque, with no negative remodeling seen (plaque increase: CBS Vs LA, HA, C, $p = 0.045$). No patients with edge restenosis after catheter – based radiation was seen in our series of patients.

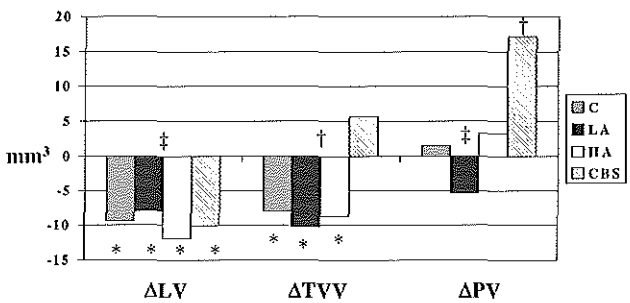

Figure 2.
Changes in volumes at the stent edge
* = p<0.05, post vs follow-up, † = between groups: $p < 0.05$.
‡ = p is not significant for ΔLV all groups and for Δ PV in C, LA and HA.

Table 4. Mean (SD) volumes for the stent

Stent (mm^3)	LV Post	LV* F/UP	TVV Post	TVV F/UP	PBS Post	PBS F/UP	NIH
C	113.9 (29.7)	92.8 (28.7)	256.1 (73.2)	257.3 (67.4)	142.2 (54.1)	143.7 (49.4)	20.8 (11.5)
LA	127.3 (42.6)	105.5 (40.1)	266.6 (96.5)	264.5 (98.3)	139.3 (59.1)	137.8 (63.7)	21.2 (12.1)
HA	122.4 (20.0)	111.7 (24.3)	267.8 (66.9)	265.3 (65.1)	145.4 (49.1)	144.6 (45.3)	9.0 (8.6)†
CBS	128.6 (41.3)	121.8 (41.6)	258.9 (73.6)	278.0 (89.8)*	130.3 (34.2)	149.3 (49.8)*	6.9 (6.6)†

* = $p < 0.05$ Post vs Follow-up. † = $p < 0.05$ between groups ANOVA.
No significant difference between groups was seen at baseline (post).

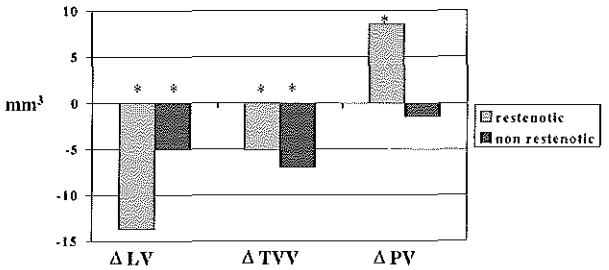

Figure 3
Restenotic edges vs Non-Restenotic (6.0-12.0μCi activity level stents).
Note greater lumen loss seen in the restenotic group. This is caused by an increase in plaque ($p<0.05$) and a less profound decrease in TVV ($p<0.05$). ΔTVV is similar in both groups.
Δ = change in volume (post vs follow-up), * = $p<0.05$ post vs follow-up.

Stent activity and dose prescribed

Mean stent activity at implantation (LA) was 1.1 +/- 0.3 uCi. Mean stent activity at implantation (HA) was 8.6 +/- 1.6 uCi. For CBS mean dose prescribed was 16.7 +/-2.0 Gy.

Discussion

The development of NIH within the stent witnessed at 6 – month follow – up is well appreciated[15], however the changes that occur at the stent edges or indeed behind the stent struts have not been the focus of attention until recently[4]. This paper is the first describing the difference in vascular remodeling seen after radioactive stent implantation and catheter – based radiation plus stenting, using modern conventional stents as a benchmark. The key findings are as follows:

The degree of inhibition of NIH after the implantation of a radioactive stent with activity of 6.0-12μCi and CBS was similar.

There was no significant remodeling behind the stent after conventional or radioactive stent implantation; however the CBS group demonstrated both an increase in plaque behind the stent and TVV.

At the stent edge three patterns of remodeling are seen at 6 – month follow - up: firstly a shrinkage in TVV and LV after C and LD radioactive stent implantation. These two subgroups were not associated with stent edge restenosis in this series. After HD stent implantation a pattern similar to C and LD is seen in those edges that remain non – restenotic, however in restenotic edges plaque increase is the major contributor to lumen loss. In the CBS group a similar lumen loss to the other groups is seen, however this occurs secondary to an increase in plaque and without a loss in TVV.

Neointimal Hyperplasia

In our study neointimal formation was inhibited after higher dose radioactive stent implantation and after catheter - based radiation plus stenting. The former contrasts with the recent study by Carter et al. using ^{32}P stents in the porcine model[16], but is in keeping with earlier studies of Hehrlein[6] using the rabbit model and recent reports by Albiero[4] in which a dose – dependent inhibition of NIH was noted.

Mechanism of remodeling behind the stent

Catheter–based radiation

After conventional and radioactive stent implantation little positive or negative remodeling is witnessed behind the stent. In stark contrast to this, is the increase in plaque behind the stent and TVV seen after catheter – based radiation and stenting. Part of the key to understanding this process may be acquired from understanding the healing process after BA. Wilcox and co – workers[17,18] describe the presence of early proliferation of myofibroblasts expressing contractile proteins in the adventitia surrounding the porcine coronary artery after BA. Tracing studies have indicated that the same cells migrate and form part of the neointima. Wilcox hypothesizes that the adventitial myofibroblasts constrict the artery at the angioplasty site much in the same way as myofibroblasts participate in scar retraction in dermal healing. The source of these myofibroblasts may be distant to the immediate site of injury including pericardial, adipose and intra-myocardial layers[19].

Radiation treatment of porcine coronary arteries after BA up - regulates p21 synthesis in adventitial cells, especially myofibroblasts. Such induction is dose – dependent and sustained for at least 7 days after radiation. Additionally radiation inhibits the expression of growth factors, reduces proliferation of adventitial myofibroblasts, decreases the production of α - actin by the adventitial myofibroblasts, preventing the formation of the myofibroblast scar around the angioplasty site and negative vascular remodeling[17,20]. Data from Fareh and co – workers[21] suggest that inhibition of migration but not of cellular proliferation may occur at lower doses of radiation. Therefore cells may remain in situ, unable to migrate but able to grow in the presence of a weakened external elastic membrane. After one week the effect of the radiation diminishes and cellular proliferation, possibly as a reaction to the presence of the stent, continues behind the stent in the context of positive vascular remodeling. In our cohort of patients no cases of stent malapposition were seen at follow – up although our group has described this as a risk of ongoing positive vascular remodeling[22,23].

Radioactive stent

The objective of using the radioactive stent is not to neutralise myofibroblasts in the adventitia. Rather it is the prevention of the migration and invasion of myofibroblasts from the adventitia through the stent struts and into the lumen. As is seen in the HA group this is accomplished due to the continuous and low dose rate provided by the radioactive stent. Due to the range of the 'radioactive fence' created, adventitial cells remain intact without upregulation of growth factors and inhibition of contractile proteins. Consequently no remodeling is seen behind the radioactive stent at either activity level.

Edge Remodeling

Hoffman[15] has previously described negative remodeling at the stent edge and of the stent/vessel wall after conventional stent implantation. In our study we have been able to precisely describe the decrease in TVV as the dominant contributor to non – restenotic lumen loss at the stent edge and to confirm the absence of recoil and remodeling in modern stents at 6-month follow – up. Recent reports suggest that the edge effect and edge restenosis may be due to an increase in plaque at the edge and to a component of negative remodeling as one moves axially

from the stent[4]. However, the edge response after catheter – based radiation and subsequent conventional stent implantation were undefined until the current paper.

Edge restenosis: is this the result of low – dose radiation?

Radioactive stents have a limited radioactive range of effect. Whereas those cells behind the stent struts may be well fenced at the doses discussed, cells proximal and distal to the extremity of the stent, in injured areas treated by the balloon (up to 3mm outside the stent)[24], may not be effectively covered by the range of the stent radiation. The latter phenomenon is a further example of geographical miss[25]. Whether there is a proliferative effect on tissue secondary to low – dose radiation at the edge of the radioactive stent has yet to be proven in clinical trials. Certainly there is evidence from animal work that low dose radiation may induce a proliferative effect on tissue[26]. If the edge restenosis is the result of an aberrant response by non-injured healthy or diseased tissue subjected to radiation, then this may suggest that low-dose radiation has a stimulatory effect on non-injured tissue.

Implications for the future: Dealing with the edge effect

If the edge effect is the result of balloon-induced trauma and low dose radiation then limiting the trauma outside the stent and expanding the irradiated area beyond the injured area should be attempted. For radioactive stents conceivably the most practical approach may be to extend the area of irradiation beyond the injured area using a 'hot-end stent'. This involves literally concentrating the greatest activity of the stent at the stent edges; such stents are already undergoing multicenter trials.

If the edge restenosis were purely the result of negative remodeling induced by low-dose radiation in an injured area, then the lengthening of the stent by a non – radioactive, cold – end would be a logical solution to prevent remodeling at the extremities. If plaque constitutes a large percentage of the healing process manifested by the restenosis then cold-end stent implantation is unlikely to work as neointimal proliferation may occur at the edges of the radiation within the stent (an in-stent candy-wrapper).

In the event that excessive vascular remodeling is present after catheter – based radiotherapy, then a self – expanding stent may play a useful role. The appeal here is that via direct stenting the injury caused by balloon pre - dilation will be avoided and the self expanding stent would be permitted to expand, minimizing geographical miss and stent malapposition[22,23].

Limitations

This was a retrospective, non – randomised study of individuals who had completed 6 – month follow – up and in whom IVUS examination was possible. Individuals who had a total occlusion or in whom the IVUS catheter could not be passed under acceptable clinical circumstances were not included.

No edge restenosis was seen in the CBS group, unlike in the HA radioactive stent group, however both the CBS and the HA radioactive stent groups reflected the larger parent populations from which they were selected in all other features.

The dosimetry (catheter – based) described in this paper relates to prescribed doses only and does not necessarily reflect the dose delivered 2mm from the source in the adventitia. Description of dosimetry is beyond the scope of this paper, however previous work by the authors, using a similar radiation source and study population, suggests that delivered dose, residual plaque

burden and tissue composition play a fundamental role on the volumetric outcome at 6-month follow-up after catheter – based ß-radiation therapy and BA[25].

Conclusion

Distinct differences in the patterns of remodeling exist between conventional, radioactive and catheter – based radiotherapy with stenting. Users of radiation need to be alerted to the deleterious remodeling seen at the stent edges after higher – dose radioactive stent implantation and behind the stent after catheter – based radiation and stenting.

Radiation, whether it be catheter or stent – based has forced the interventional community to look closely not only at effective inhibition of intimal proliferation but also the adverse response of the artery to the combination of injury and radiation.

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CHAPTER 11

Late Coronary Occlusion after Intracoronary Brachytherapy.

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Late Coronary Occlusion After Intracoronary Brachytherapy

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Background—Intracoronary brachytherapy appears to be a promising technology to prevent restenosis. Presently, limited data are available regarding the late safety of this therapeutic modality. The aim of the study was to determine the incidence of late (>1 month) thrombosis after PTCA and radiotherapy.

Methods and Results—From April 1997 to March 1999, we successfully treated 108 patients with PTCA followed by intracoronary β-radiation. Ninety-one patients have completed at least 2 months of clinical follow-up. Of these patients, 6.6% (6 patients) presented with sudden thrombotic events confirmed by angiography 2 to 15 months after intervention (2 balloon angioplasty and 4 stent). Some factors (overlapping stents, unhealed dissection) may have triggered the thrombosis process, but the timing of the event is extremely unusual. Therefore, the effect of radiation on delaying the healing process and maintaining a thrombogenic coronary surface is proposed as the most plausible mechanism to explain such late events.

Conclusions—Late and sudden thrombosis after PTCA followed by intracoronary radiotherapy is a new phenomenon in interventional cardiology. (*Circulation*. 1999;100:789-792.)

Key Words: thrombosis ■ angioplasty ■ radioisotopes

Thrombotic occlusion after PTCA is associated with increased morbidity and mortality rates.[1] Current techniques of stenting followed by antiplatelet therapy have dramatically reduced the incidence of this event to <1.5%.[2,3]

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Intracoronary radiation is a promising new therapy to prevent restenosis. Recent randomized trials demonstrated a reduction in the restenosis rate and maintenance of benefits up to 2-year follow-up.[4–6] Presently, limited data are available regarding long-term safety after intracoronary brachytherapy.[5,7] Although subacute thrombosis has been reported after radiotherapy,[4,8,9] the incidence of late thrombotic events has not been determined.

The aim of this study was to document the incidence of late (>1 month) thrombotic events after elective PTCA followed by intravascular radiotherapy.

Methods and Results

From April 1997 to March 1999, 108 consecutive patients were successfully treated with catheter-based intracoronary β-radiation at the Thoraxcenter (Rotterdam, The Netherlands). The Medical Ethical Committee approved the use of radiation therapy and informed consent was obtained from every patient. All patients presented with stable angina pectoris and single vessel disease. Brachytherapy was performed using the Beta-Cath system (Novoste Corporation)[10] (n=76 patients, 32 stents and 44 balloon angioplasty [BA]), or the Guidant intravascular brachytherapy system (Guidant Corporation Vascular Intervention)[11] (n=32 patients, 13 Stents and 19 BA). BA and stenting were performed according to standard techniques. Intravascular ultrasound (IVUS) was performed after radiation with a mechanical ultrasound catheter (CVIS, Boston Scientific). Off-line quantitative coronary angiography was performed using CAAS system (Pie Medical Imaging BV). Six-month angiographic and IVUS follow-up was scheduled in all patients.

All patients were discharged without complications. Ninety-one patients completed at least 2-month clinical follow-up. We observed 1 case of subacute thrombosis occurring 15 days after stenting. This patient received an 18-mm long stent (postdilated at 10 atm) with optimal IVUS result. Ticlopidine withdrawal (12 days after stenting) was the plausible explanation of thrombosis in this case.

Six patients (6.6%) presented with sudden late thrombotic coronary occlusion. Two of them were treated with BA and the remaining 4 received an additional stent after radiation. Their clinical characteristics are summarized in

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Clinical and Angiographic Variables

Variables	1	2	3	4	5	6
Age, y	57	58	49	73	52	62
Sex	Male	Female	Male	Female	Female	Female
Pre-procedure						
Target vessel	LCX	RCA	LCX	LAD	RCA	RCA
Type of lesion	B	B	B	A	A	B
RD, mm	2.5	2.8	2.67	2.66	2.84	2.6
MLD, mm	0.9	1.12	0.64	1.09	0.65	0.55
DS, %	66	60	76	60	77	78
Lesion length, mm	13	15	18	11.2	9.6	9.7
Procedure						
Brachytherapy system	Beta-Cath	Guidant	Beta-Cath	Beta-Cath	Beta-Cath	Beta-Cath
Source length, mm	30	27	30	30	30	30
Prescribed dose, Gy	12*	35†	12*	14*	18*	14*
Stent/angioplasty	Stent	Balloon	Balloon	Stent	Stent	Stent
Total stent length, mm	41			25	25	16
Postprocedure						
Dissection/type	No	Yes/B	Yes/B	No	No	No
MLD, mm	2.47	2.07	2.15	2.4	2.34	2.4
DS, %	−1	26	21	9.5	17	7
Clinical success	Yes	Yes	Yes	Yes	Yes	Yes
Follow-up						
Event	VF	Inferior MI	Postlateral MI	Anterior MI	Inferior MI	Inferior MI
Time, mo	2	3	15	10	3	2.5
Antiplatelet medication	Yes	Yes	Yes	No	Yes	Yes
Associated factors	Long stent	Dissection	Dissection at 6-mo	Aspirin withdrawal	No	No

LCX indicates left circumflex artery; RCA, right coronary artery; LAD, left anterior descending artery; RD, reference diameter; MLD, minimal lumen diameter; DS, diameter stenosis; VF, ventricular fibrillation; and MI, myocardial infarction.
*At 2 mm from the source; †at 0.5 mm into the vessel wall.

the Table. No clinical or anatomic characteristic appeared to be related to these events.

In patient 1, overlapping 9- and 32-mm NIR stents (Medinol Ltd) were optimally implanted as assessed by IVUS. Patients 2 and 3 (BA) showed type B dissections without compromising flow postprocedure. Patients 4 and 5 both received a Multilink 25-mm stent (Advanced Cardiovascular Systems/Guidant), and patient 6 received a NIR 16-mm stent with optimal angiographic results. Stent patients were discharged on aspirin (250 mg/d) and ticlopidine (250 mg BID for 15 days in patients 3 and 4, and for 30 days in cases 5 and 6). BA patients received aspirin alone.

Patient 1 was readmitted with ventricular fibrillation 2 months after the procedure, whereas, patients 2, 5, and 6 sustained inferior myocardial infarctions (MI) between 2.5 and 3 months after the treatment. The irradiated segment was occluded at 6-month angiogram in patients 1 and 2 (Figure 1). Thrombotic occlusion was successfully treated by primary angioplasty in patients 5 and 6.

In patient 3, the 6-month IVUS control revealed a persistent (unhealed) submedial dissection (Figure 2) with no signs of restenosis. Nine months later, this patient sustained a posterolateral MI which was treated with thrombolytics. Two weeks after this treatment, an angiogram performed because of recurrent angina showed the occlusion in the irradiated area. Similarly, the 6-month IVUS control of patient 4 showed no neointimal hyperplasia. Four months after control, she had a stroke and aspirin was replaced by acenocoumarol. Ten days later, she sustained an anterior MI. The thrombotic occlusion in the treated site was confirmed by angiography.

Discussion

Progression to total occlusion after BA is a stable process in the general nonirradiated population which occurs in approximately 4% of patients, leading to a MI in <0.5%.[12] In contrast, our study shows a high incidence (6.6%) of thrombotic clinical events 2 to 15 months after PTCA and brachytherapy.

Coronary dissection after BA is associated with abrupt closure; however, type B dissections (NHLBI classification), as observed after BA in our patients, have not been related to thrombotic events.[13] The normal healing process, present after dissections, may be impaired after intracoro-

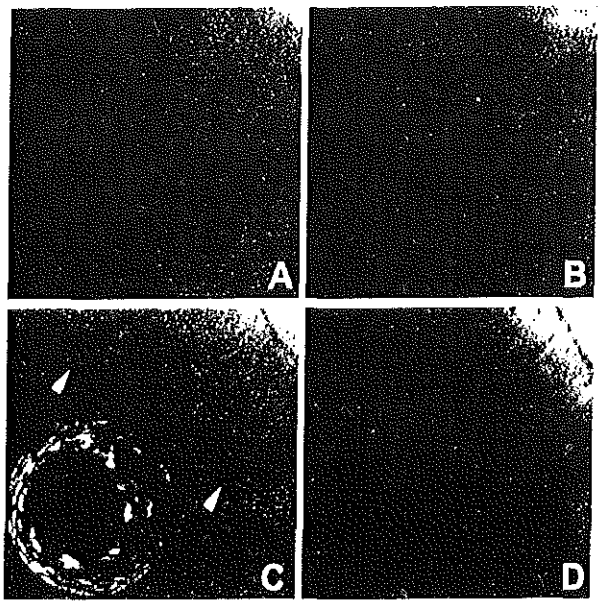

Figure 1. Patient 1. A, Preprocedure angiography shows a significant lesion in the mid-third of left circumflex artery. B, Radioactive source placed in treated site. C, Postprocedure angiography and IVUS images show an optimal result (arrowheads). D, At 2 months, the proximal part of stent appeared occluded.

nary radiation.[14] Whether unhealed dissections, as demonstrated in patient 3, is related to late thrombosis remains to be elucidated in a larger population. Further, the necessity of stenting mild dissections without compromising flow after radiotherapy should be investigated.

The mean time of subacute thrombosis after stenting is approximately 5 to 6 days.[2,3] In a recent study, subacute thrombosis occurred within the first 24 hours in 86% of patients treated with aspirin and ticlodipine for 14 days, with no case of thrombotic events occurring after 15 days.[15] Colombo et al reported only 2 cases (0.6%) of thrombosis occurring 2 to 6 months after stenting.[2] In contrast, in our study, 4 patients receiving a stent (8.8%) experienced thrombosis late after radiation.

Experimentally, reendothelialization after injury takes >4 weeks to be completed.[16] However, the clinical presentation of subacute thrombosis infrequently occurs later than 15 days after stenting,[15] when the reendothelialization process may still be incomplete. Delayed reendothelialization as a trigger mechanism of late stent thrombosis after antineoplastic therapy has been hypothesized previously.[17] Farb et al reported incomplete endothelialization 3 months after placement of β-radioactive stent.[18] Nevertheless, the same group showed no differences regarding endothelial cell growth between radioactive and control stents in another experimental model.[19] Further studies should address the timing of stent reendothelialization after brachytherapy to determine its role on the pathogenesis of late thrombosis.

Although multiple stents have been related to subacute thrombosis,[20] the significance of multiple stent implantation (patient 1) on late thrombotic phenomena has not been demonstrated.

The use of intracoronary β-radiation is a common feature in our patients. However, the judgment of whether radiation is the key factor in the pathogenesis of late thrombosis should await the analysis of ongoing trials. Concomitantly, the benefit of prolonged antiplatelet therapy with the combination of aspirin, clopidogrel, or ticlopidine should be considered.

Limitations

Our patients were included in well-controlled β-radiation studies with similar baseline characteristics and inclusion criteria (lesion length <15 mm, treatment of single vessel). However, 2 different systems to deliver β-radiation were used.

In addition, it is not possible to rule out the natural history of coronary disease as a cause of late thrombosis. However, the incidence of total occlusion in the general nonirradiated population is much lower than that observed in our study. In fact, the incidence of late thrombotic events would be even higher if, in the interest of completeness, we waited for 1-year follow-up in the total patient population.

Finally, whether late thrombosis is a generic complication of intracoronary radiotherapy or is restricted to the use of β-sources cannot be extrapolated from our findings.

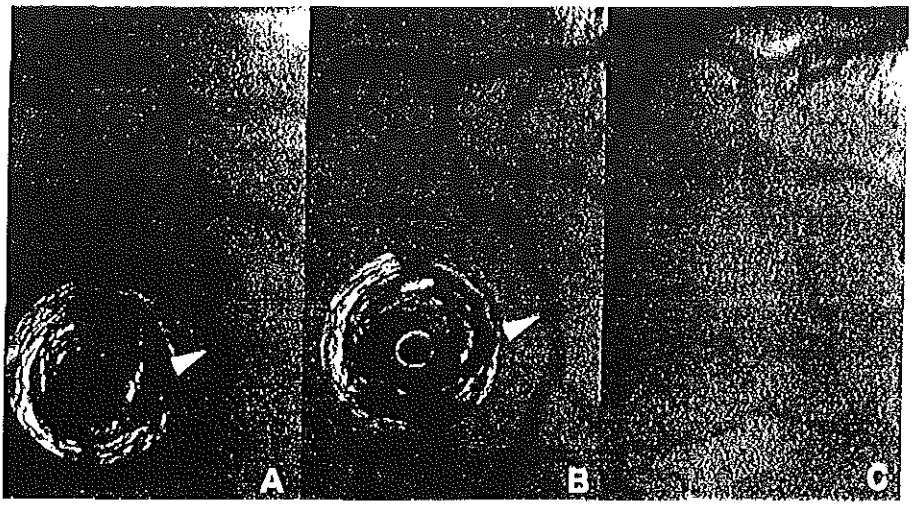

Figure 2. Patient 3. A, Postprocedure coronary dissection, demonstrated both on angiography and IVUS, did not compromise flow in treated area (arrowhead). B, This dissection persisted unhealed at 6-month control (arrowhead). C, At 15 months, irradiated segment appeared occluded.

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CHAPTER 12

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.

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*

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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,*

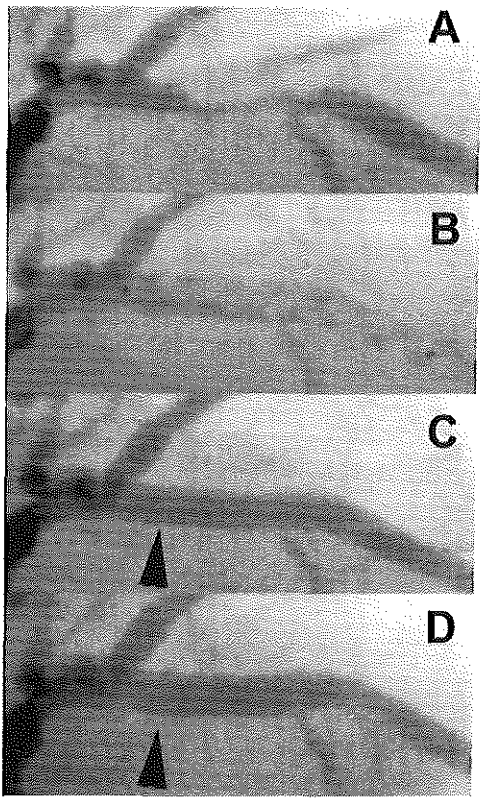

Figure 1. **(A)** *Pre-procedure angiogram shows the stenosis in the proximal segment of the left anterior descending artery;* **(B)** *centering balloon inflated during irradiation;* **(C)** *post-procedure angiogram (arrowhead indicates the location where stent malapposition appeared at follow-up);*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

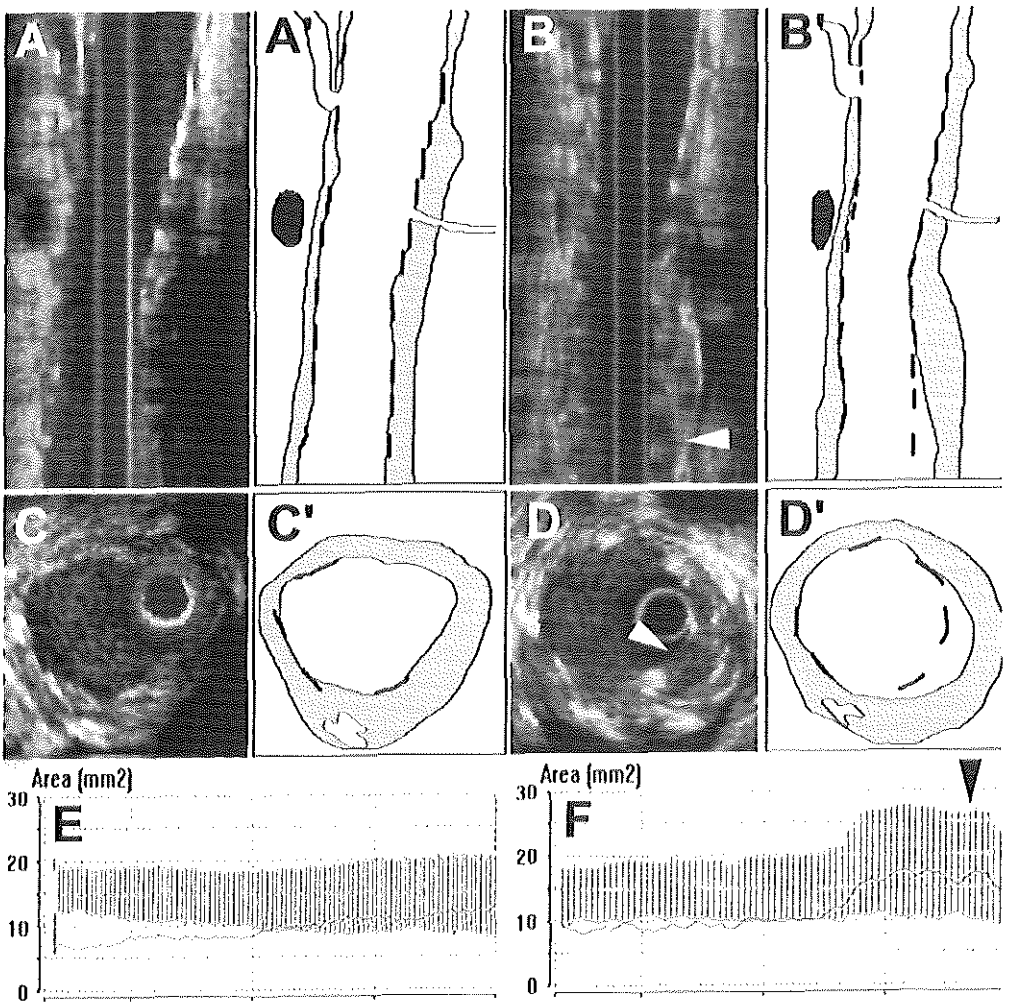

Figure 2. *(A) Longitudinal view of 3-D intravascular ultrasound (IVUS) image reconstruction at baseline; (A') schematic model of 3-D IVUS image reconstruction at baseline; (B) longitudinal view of 3-D reconstruction IVUS image at follow-up (arrowhead indicates the malapposition site); (B') schematic 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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CHAPTER 13

The Outcome from Balloon-Induced Coronary Artery Dissection After Intracoronary β-Radiation.

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Outcome from balloon induced coronary artery dissection after intracoronary β radiation

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Abstract

Objective—To evaluate the healing of balloon induced coronary artery dissection in individuals who have received β radiation treatment and to propose a new intravascular ultrasound (IVUS) dissection score to facilitate the comparison of dissection through time.

Design—Retrospective study.

Setting—Tertiary referral centre.

Patients—31 patients with stable angina pectoris, enrolled in the beta energy restenosis trial (BERT-1.5), were included. After excluding those who underwent stent implantation, the evaluable population was 22 patients.

Interventions—Balloon angioplasty and intracoronary radiation followed by quantitative coronary angiography (QCA) and IVUS. Repeat QCA and IVUS were performed at six month follow up.

Main outcome measures—QCA and IVUS evidence of healing of dissection. Dissection classification for angiography was by the National Heart Lung Blood Institute scale. IVUS proven dissection was defined as partial or complete. The following IVUS defined characteristics of dissection were described in the affected coronary segments: length, depth, arc circumference, presence of flap, and dissection score. Dissection was defined as healed when all features of dissection had resolved. The calculated dose of radiation received by the dissected area in those with healed versus non-healed dissection was also compared.

Results—Angiography (type A = 5, B = 7, C = 4) and IVUS proven (partial = 12, complete = 4) dissections were seen in 16 patients following intervention. At six month follow up, six and eight unhealed dissections were seen by angiography (A = 2, B = 4) and IVUS (partial = 7, complete = 1), respectively. The mean IVUS dissection score was 5.2 (range 3–8) following the procedure, and 4.6 (range 3–7) at follow up. No correlation was found between the dose prescribed in the treated area and the presence of unhealed dissection. No change in anginal status was seen despite the presence of unhealed dissection.

Conclusion—β radiation appears to alter the normal healing process, resulting in unhealed dissection in certain individuals. In view of the delayed and abnormal healing observed, long term follow up is indicated given the possible late adverse effects of radiation. Although in this cohort no increase in cardiac events following coronary dissections was seen, larger populations are needed to confirm this phenomenon. Stenting of all coronary dissections may be warranted in patients scheduled for brachytherapy after balloon angioplasty.

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Keywords: dissection; intravascular ultrasound; angiography; coronary artery; brachytherapy; angioplasty

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Despite excellent acute results, restenosis at six month follow up after coronary artery balloon angioplasty remains a serious problem.[1] Excessive neointimal formation, extracellular matrix synthesis, and negative vessel remodelling in response to balloon injury have been documented as the main mechanisms of restenosis.[1 2] Intracoronary radiation treatment has recently emerged as a means of preventing and treating restenosis in coronary arteries treated by balloon angioplasty. The theoretical benefit of radiation in preventing neointimal proliferation resides in the destruction of more rapidly dividing smooth muscle cells.[3 4] It may not be surprising that by inhibiting the above deleterious features of healing after balloon angioplasty, intracoronary radiation may also alter normal healing processes.

Coronary artery dissection is common after balloon angioplasty. This is angiographically visible in 20–45% of cases following balloon angioplasty[5] and present in up to 85% of cases when intravascular ultrasound (IVUS) assessment is used.[6] If further angioplasty of the lesion is not undertaken, then it is recognised that nearly all angiographic dissection will heal over a six month time frame.[5 7] Whether intracoronary radiation will prevent the process of natural healing after balloon induced dissection has not been documented thus far in humans. To examine this, we retrospectively analysed coronary artery dissections using angiography and IVUS, at the time of treatment and at six month follow up, in patients treated with intracoronary radiation following balloon angioplasty. We also aimed to compare the prescribed dose received by the treated area in individuals with non-healing dissection with the dose received by those individuals with healed dissection.

Methods

PATIENT SELECTION

Patients eligible for the study were those treated successfully with balloon angioplasty followed by intracoronary irradiation according

Table 1 IVUS dissection score

Arc	*Length*	*Depth*	*Flap*
< 90° = 1	< 5 mm = 1	Partial = 1	Yes = 1
90–180° = 2	5–10 mm = 2	Complete = 2	No = 0
> 180° = 3	> 10mm = 3		

Table 2 Baseline characteristics (n = 22)

Mean (SD) age (years)	55.7 (9.3)
Coronary risk factors	
Smoking (n (%))	15 (68)
Hypercholesterolaemia (n (%))	12 (55)
Family history (n (%))	12 (55)
Hypertension (n (%))	11 (50)
Diabetes (n (%))	6 (26)
Treated vessel	
LAD (n (%))	12 (55)
LCX (n (%))	6 (26)
RCA (n (%))	4 (18)
Prescribed dose	
16 Gy (n (%))	9 (41)
14 Gy (n (%))	5 (23)
12 Gy (n (%))	8 (36)

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

to the beta energy restenosis trial (BERT-1.5). The purpose of this trial was to evaluate the safety and efficacy of low dose β source irradiation following balloon angioplasty with and without stent implantation in patients with single "de novo" lesions of native coronary arteries. The design of this trial was a prospective multicentre non-randomised feasibility study. We used a strontium 90 (^{90}Sr) source with yttrium as a pure β emitter, and patients were randomised to receive 12, 14, or 16 Gray (Gy). The inclusion and exclusion criteria of this trial have been previously reported.[14]

RADIATION DELIVERY SYSTEM

The Beta-Cath system (Novoste Corp, Norcross, Georgia, USA) was used to deliver localised β radiation to a coronary artery at the site of coronary intervention. The device consists of three components: (1) the transfer device which stores the radiation source train and allows the positioning of these sources within the catheter; (2) the delivery catheter, which is a 5 F multilumen over the wire non-centred catheter which uses saline solution to send and return the radiation source train; and (3), the radiation source train consisting of a series of 12 independent cylindrical seeds which contain the radioisotope ^{90}Sr sources and is bordered by two gold radiopaque markers separated by 30 mm.[15]

IVUS IMAGE ACQUISITION ANALYSIS SYSTEM

The segment subject to analysis was examined with a mechanical IVUS system (ClearView, CardioVascular Imaging System (CVIS), Sunnyvale, California, USA) with a sheath based IVUS catheter incorporating a 30 MHz single element transducer rotating at 1800 rpm. The transducer is placed inside a 2.9 F 15 cm long sonolucent distal sheath which alternatively houses the guidewire (during the catheter introduction) or the transducer (during imaging, after the guidewire has been pulled back). To assure the correct identification and analysis of the irradiated segment, certain steps were followed. First, an angiogram was performed after positioning the delivery catheter, and the relation between anatomical landmarks and the two gold markers was 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 motorised IVUS pullback, all side branches were counted and the guiding landmark was identified. The correct selection of the marker was confirmed by visualising the position of the IVUS probe during a contrast injection. Once the acquisition was completed, we selected the segment of interest by taking the digitised cross-sectional images proximal or distal to the guiding landmark up to 30 mm, which is the area encompassed by the two gold markers of the radiation source. At follow up, we selected the same region of interest and compared it with that after treatment.

PROCEDURE

The medical ethics committee of the Erasmus Medical Center, Rotterdam approved the study and all patients signed a written informed consent form. In the BERT-1.5 trial balloon angioplasty was performed according to standard clinical practice. Following successful angioplasty, patients were randomised to receive 12, 14, or 16 Gy, as calculated at 2 mm from the centre of the radiation source. The 5 F delivery catheter of the Beta-Cath

Table 3 Angiographic parameters pre- and postintervention and at six month follow up for patients with dissection

		Pre-procedure	*Postprocedure*				*Follow up*				
Patient	*Dose prescribed*	*MLD*	*Dissection grade*	*RD*	*DS (%)*	*MLD*	*Dissection grade*	*RD*	*DS (%)*	*MLD*	*LLI*
1	12	0.77	C	2.58	40	1.56	–	2.41	32	1.63	−0.09
2	14	1.23	A	2.72	17	2.25	–	2.84	8	2.60	−0.34
3	12	0.78	B	2.44	26	1.80	–	2.77	36	1.77	0.02
4	12	0.78	B	3.17	31	2.18	–	3.11	44	1.75	0.31
5	14	1.21	B	3.21	34	2.12	B	3.32	35	2.15	−0.03
6	16	0.82	A	2.73	30	1.92	A	3.01	52	1.44	0.11
7	16	0.96	B	2.40	23	1.85	B	2.94	23	1.58	0.31
8	16	1.42	C	2.82	25	2.12	–	2.96	54	1.41	0.97
9	16	0.88	C	2.18	29	1.53	–	2.16	19	1.10	0.67
10	16	1.11	C	3.08	28	2.19	A	3.25	54	1.50	0.81
12	12	1.06	A	2.62	3	2.54	–	3.21	75	0.81	1.17
13	12	1.17	A	2.82	29	2.00		3.27	65	1.11	1.01
16	16	1.33	B	3.21	22	2.49	B	3.39	31	2.35	0.12
17	14	1.36	B	2.49	25	1.87	–	2.79	13	2.44	−1.14
19	12	0.61	B	2.68	21	2.12	B	2.80	31	1.94	0.12
20	12	1.70	A	4.69	44	2.63	-	3.86	29	2.75	−0.13
Mean	13.9	1.09		2.92	27.31	2.09		2.95	39.25	1.77	0.27

MLD, minimal luminal diameter; RD, reference diameter; DS, diameter stenosis; LLI, late loss index

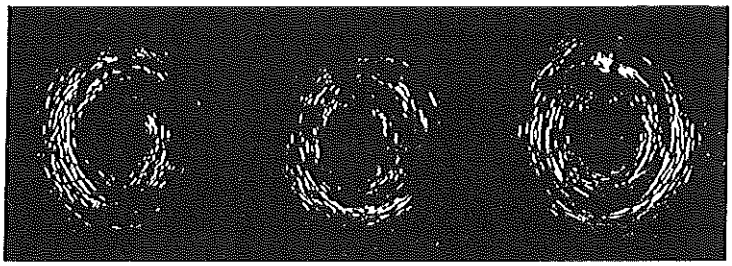

Figure 1 Intravascular ultrasound images (left and centre) showing a double lumen between 12 and 1 o'clock postintervention. The right image shows the same lesion at six month follow up with the unhealed false lumen seen between 11 and 2 o'clock.

system was inserted over the guidewire and advanced such that the two marker bands encompassed the angioplasty site. The guidewire was removed and the radiation source train containing 12 ^{90}Sr seeds was positioned between the gold markers using fluoroscopic visualisation. The seeds remained in place for 2.5–3.5 minutes to deliver the assigned dose of radiation. Following irradiation, repeat angiography and IVUS pullback were performed. Intracoronary nitrates were administered before the treated artery was examined with IVUS. The 2.9 F IVUS catheter (CVIS, Sunnyvale) was advanced distal to the treated site. A continuous motorised pullback at a speed of 0.5 mm/s was carried out, followed by an angiographic control. At six month angiographic follow up, identical quantitative coronary angiography (QCA) and IVUS examination of the treated area was performed.

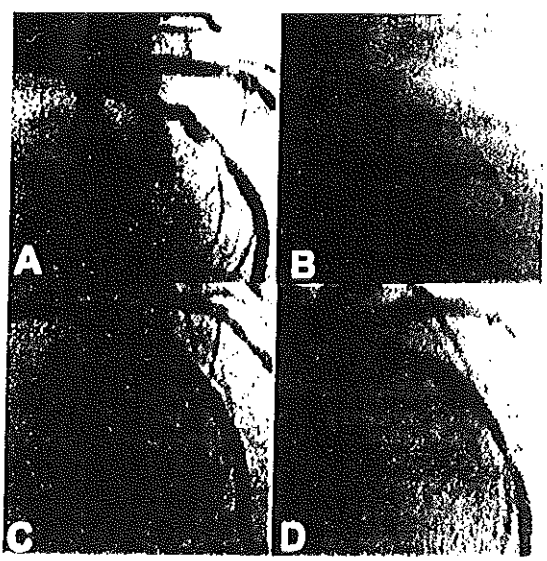

Figure 2 Coronary angiogram showing:-(A) lesion precatheter; (B) radioactive source in situ; (C) postintervention; and (D) the same lesion at six month follow up. Note the presence of an edge effect and absence of angiographic dissection at six month follow up.

DEFINITIONS

Dissection was defined both angiographically and by IVUS. Angiographic dissection was defined using the National Heart Lung and Blood Institute criteria for the classification of dissection.[18] QCA analysis was performed before the intervention, after treatment, and at six month follow up using identical gantry positions. Coronary angiography was performed after intracoronary administration of nitrates. The offline analysis of at least two orthogonal projections was performed by means of the cardiovascular angiography analysis sytem (CAAS II, Pie Medical BV, Maastricht, The Netherlands). Calibration of the system was based on dimensions of the catheters not filled with contrast medium. This method of analysis has been previously validated.[20 21] The following measurements were obtained in each projection: minimal luminal diameter (MLD), reference diameter, % diameter stenosis, and lesion length. Lesion length was user defined and not done by an algorithm using curvature analysis of the diameter function. The reference diameter was obtained by an interpolated method. Acute gain was defined as MLD measured after treatment minus MLD preintervention. Late loss was defined as MLD after treatment minus MLD at follow up. Late loss index was defined as late loss divided by acute gain. Restenosis was defined as > 50% diameter stenosis at follow up and located within the treated area.

IVUS dissection was defined as a longitudinal tear parallel to the vessel wall.[1] In all patients with IVUS detected dissection, length, arc, and depth were recorded. For inclusion in the study all dissections were located within the area treated by radiation. Axial length was measured in millimetres. Circumferential extension was measured as an arc in degrees. The maximal depth of wall disruption was defined as follows: partial plaque between tear and adventitia; complete full thickness tear extending through the plaque to the adventitia.[1]

An IVUS dissection score was created to rank the severity of dissection (table 1). This score facilitates comparison of dissection after the procedure and at follow up. Assuming that a dissection is present, the potential range of the dissection score was 3–9. The dissection was considered to be healed when all features

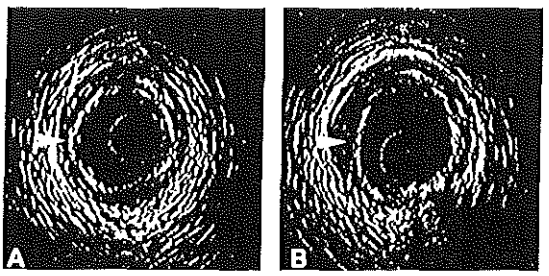

Figure 3 This IVUS image correlates with the angiogram in fig 2. The arrowheads show the presence of an intact lumen (A) and an unhealed flap (B), corresponding to the same area.

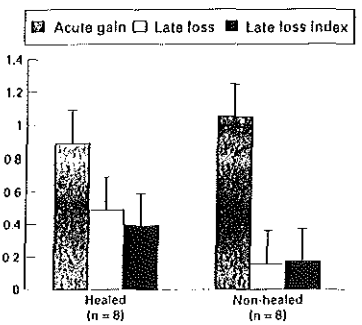

Figure 4 QCA analysis of healed versus non-healed dissection (p = NS).

of dissection had disappeared. Partial healing was considered to have occurred when at least one feature of dissection persisted at follow up. Absence of healing was defined as no change to the dissection on follow up.

The prescribed radiation dose delivered to 2 mm from the source was recorded and compared between individuals with and without healed dissection.

STATISTICAL ANALYSIS

Quantitative data are presented as mean (SD). The non-paired two tailed Student's *t* test was used to compare dose levels and healed/non-healed dissection.

Results

BASELINE CHARACTERISTICS

From April to December 1997, 31 patients were treated at our institution according to the BERT 1.5 trial. Eight patients, who received stent implantation because of important recoil or angiographic and IVUS proven dissection after balloon angioplasty, were excluded from the assessment. One patient refused IVUS at follow up; the same patient had no evidence of dissection following treatment. Therefore the study population was 22 patients. The baseline characteristics of the patients are shown in table 2.

CLINICAL, ANGIOGRAPHIC, AND IVUS FOLLOW UP

At follow up 14 patients (63%) remained asymptomatic. Six patients presented with stable angina pectoris: one with Canadian Cardiovascular Society (CCS) class 1 angina, one with CCS class 2, and four with CCS class 3. The follow up angiography demonstrated restenosis (> 50% diameter stenosis on quantitative coronary angiography) in five patients (24%). These included the four patients with CCS class 3 angina. One restenotic patient showed aneurysmatic formation within the irradiated area. The prescribed dose in restenotic patients was 12 Gy in one patient, 14 Gy in one patient, and 16 Gy in three patients.

Dissection was seen in 16/22 patients (73%) after intervention using both angiographic and IVUS criteria. At six month follow up dissection was seen in six patients on angiography (38%) and eight patients on IVUS (50%) (table 3). Disagreement between IVUS and angiography was caused by the presence of a double lumen in one individual (fig 1) and a flap in another (figs 2 and 3), neither of which was detected by angiography. Angiographic analysis of healed versus non-healed dissection is presented in fig 4. No difference was seen in the reference diameter, % diameter stenosis, and MLD before or after the procedure or at follow up for either the healed or the non-healed dissection groups (table 3). As

Table 4 Postintervention and six month follow up of dissection evaluated by IVUS

	Postintervention					*Follow up*				
Patient	*Arc*	*Length (mm)*	*Depth*	*Flap*	*IVUS score*	*Arc*	*Length (mm)*	*Depth*	*Flap*	*IVUS score*
1	60°	5	P	N	4	60°	5	P	N	4
2	15°	2	P	N	3	"	"	"	"	"
3	90°	5	C	N	6	"	"	"	"	"
4	60°	5	P	N	4	30°	2	P	N	3
5	90°	5	P	N	5	30°	2	P	N	3
6	180°	2	C	Y	7	180°	2	C	Y	7
7	90°	6	P	Y	6	"	"	"	"	"
8	120°	8	P	N	5	"	"	"	"	"
9	180°	3	P	N	5	180°	3	P	N	5
10	270°	25	C	N	8	"	"	"	"	
12	90°	4	P	N	4	"	"	"	"	"
13	90°	6	P	N	5	"	"	"	"	"
16	90°	7	P	N	5	90°	5	P	N	5
17	120°	6	C	N	6	"	"	"	"	"
19	90°	7	P	N	5	90°	5	P	N	5
20	120°	3	P	Y	5	120°	3	P	Y	5
Mean	112°	6.2	P = 12/16	N = 13/16	5.2	98°	3.4	P = 7/8	N = 6/8	4.6

P, partial; C, complete; N, no; Y, yes

expected late loss and late loss index were greater in the healed dissection group, but the difference was not significant. Eight patients had persisting dissection after IVUS examination—six had no evidence of healing and two had partial healing (table 4). Three of the healed dissections resulted in restenosis. The mean IVUS dissection score was 5.2 (range 3–8) after the procedure and 4.6 (range 3–7) at follow up. IVUS healed dissection received a mean prescribed dose of 14 Gy and non-healed dissection received 13.8 Gy (p value not significant).

Discussion

We describe coronary artery dissection following intracoronary radiation treatment in a group of individuals who had dissection noted angiographically and with IVUS, but who did not undergo stent implantation as the lesion appeared stable under standard clinical conditions. These dissections were not associated with any significant acute or subacute clinical sequelae. What is remarkable is that after six month follow up, six of the angiographic dissections and eight of the IVUS proven dissections persisted. In a similar patient population who had undergone conventional balloon angioplasty (n = 183), 87 patients (47%) suffered a type A–C dissection after coronary angioplasty. Only one dissection persisted at six month follow up coronary angiography (DEBATE 1 subanalysis, unpublished data, 1999).

Why should these dissections fail to heal in a predictable manner as previously described in conventional angioplasty? In an experimental model, a reduction of cell proliferation in the media and adventitia has been observed in the early phase after balloon injury and radiation treatment. Furthermore, the expression of α smooth muscle actin in the adventitia is reduced after radiation treatment, suggesting a positive effect on vascular remodelling.[21] Consequently it appears that radiation treatment is directly implicated in altering the healing process after balloon angioplasty, increasing the potential for positive remodelling,[21] arterial dilatation, and non-healing dissection.

It remains uncertain as to whether the dissections described represent permanent disruptions to the vessel wall or merely a retardation in the healing process. The possible inhibitory healing effect of radiation may diminish with time such that at a critical point there may be a further activation of the restenotic process associated with the healing of the dissection.

In an animal model, Farb and colleagues showed a reduction in neointimal formation in ^{32}P-emitting radioactive stents three months after implantation; endothelialisation was incomplete, however, with only one third of the entire intimal surface showing endothelialisation with poor formation of cell junctions.[23] As a result of incomplete or delayed endothelialisation, late thrombosis may also occur among the described dissections. It therefore would be of considerable interest to repeat IVUS assessment of individuals undergoing intracoronary radiation treatment at a later date (12–18 months postintervention) so as to see if there is evidence of persisting dissection or of wound healing/restenosis, which may present in a delayed fashion.[18]

Although the dissections did not lead to an increase of cardiac events in our population, Preisack and colleagues recently described a higher event rate in patients who suffered coronary dissections after balloon dilatation only.[22] In this study, the dissection type was highly correlated with the probability of a clinical event. Other authors have not found a difference in six month clinical event rate in patients with stable coronary dissections.[24]

We feel that additional stent implantation may be justified in patients with dissections who are about to receive brachytherapy following balloon angioplasty. This approach may be warranted even if the dissection is stable. After stent implantation in these circumstances, we feel that a long term antiplatelet regimen (> 3 months) may prove helpful in the prevention of late thrombotic occlusion, given re-endothelialisation seems to be delayed in this patient cohort.

There have been no reports on γ radiation causing interference with the healing of dissection. Compared with γ radiation a higher dose of β energy is required in the near field to deliver the prescribed dose to 2 mm. This intrinsic feature of β radiation may be causing the deleterious effect witnessed.

The IVUS dissection score was created to obtain a means of ranking and comparing dissection between postprocedural and follow up features. Up to this point, there has been no system that employs the well described features of dissection (arc, length, depth, and presence of flap) to create such a ranking. Clearly, the fate at six month follow up of IVUS proven postprocedural dissection is not well described and we must rely on evidence that is extracted from angiographic follow up data. An IVUS ranking system may be useful to describe the fate at follow up of dissection not only in the context of normal balloon angioplasty, but also after intracoronary radiotherapy.

Using the prescribed dose delivered to the total treated area there was no difference between the dose prescribed and the presence of non-healing dissection. On the one hand this relation may be genuine, on the other it may be argued that this lack of correlation results from the use of the measure of radiation received by the total vessel; this may not reflect the radiation dose received by the specific area of dissection,[20] or the radiation which is potentially transmitted down the disrupted tissue planes of the dissection. It is possible that such tissue planes may permit greater passage of radiation with deleterious consequences such non-healing or aneurysmal change. Equally, it is possible that certain tissue characteristics, such as heavy calcification, may interrupt radiation dosing to the level of the adventitia. Clearly, IVUS provides superior information to angiography in describing tissue characteristics and is likely to be an integral part in the calculation of appropriate radiation dose in the

future,[29] so as to maximise efficacy and minimise the complications of over- and underdosing.

The design of the radioactive source delivery catheter may also be relevant to its efficacy. A non-centred catheter as used in this study may lead to inhomogeneous dosing. Alternative centred devices are available; however, the issue is as yet unresolved and will be the subject of further research.[30]

LIMITATIONS

We describe the phenomenon of non-healing coronary artery dissection after balloon angioplasty in a small group of patients. The outcome of dissection in those with flow limiting dissection has not been defined, as these individuals all had stents implanted. The angiographic dissection control group for this study is historical and there is no good description in the literature on the long term outcome of those with IVUS proven dissection.

CONCLUSION

β Radiation alters the normal healing process, resulting in unhealed dissection in certain individuals. In view of the delayed and abnormal healing witnessed, long term follow up may be prudent. Although no increase in cardiac events at six months following coronary dissection was seen in this cohort, larger populations are needed to confirm this phenomenon. Stenting of all coronary dissections and the use of prolonged courses of antiplatelet agents may be warranted in patients scheduled for brachytherapy following balloon angioplasty.

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Summary and Conclusions

The mechanism of restenosis after percutaneous coronary interventions and its treatment have previously been investigated. However, due to its complexity and multifactorial nature, the pathological process leading to restenosis is incompletely understood and consequently the "magic bullet", if there will be any, has not yet been found. In the first part of this thesis we endeavor to improve our understanding of the mechanism of restenosis after plain balloon angioplasty and stenting – the current standard practice. In the second part of the manuscript, we report on a new technology aimed at preventing the occurrence of restenosis: intracoronary radiation therapy. Therefore, specific biological markers (first chapter) and the use of three-dimensional intravascular ultrasound represented fundamental tools in our investigations.

The first chapter is an overview of the complex restenosis phenomenon. In the second chapter, the relationship between inflammation, i.e. activated neutrophils expressing CD66 antigen, and lumen renarrowing after coronary stenting and balloon angioplasty was tested. Our results confirmed previous hypothesis of a beneficial role of activated neutrophils in the restenotic process after plain balloon angioplasty. The lack of relationship between activated neutrophils and lumen renarrowing after stenting suggested that this leukocyte may favorably affect the remodeling process.

The third chapter, corroborates not only those findings from previous intravascular ultrasound (IVUS) studies showing that unfavorable remodeling plays a major role in the mechanism of restenosis after balloon angioplasty, but also provides a new methodological approach to investigate the restenotic process in humans. By the use of a new technology, three-dimensional (3D) IVUS, we were able to demonstrate that: 1) the pattern of remodeling may vary within individual coronary segment, 2) the selection of the cross-section with the minimal lumen area at follow-up for serial IVUS analysis may be inaccurate since it does not reflect the location of maximal lumen loss (i.e., the maximal restenotic reaction). In chapter 4, we demonstrated, using volumetric IVUS-3D quantification of the entire stented segment, that the restenotic process after implantation of two new generations tubular stents are exclusively due to neointimal formation. In spite of differences in design and strut thickness, MULTILINK(and NIR(stents, both recently approved by the FDA, were able to maintain their radial support over six months (i.e. no stent recoil) and elicited similar amount of neointimal proliferation.

In the second part, chapter 5 reports on the clinical application of a new therapy developed to reduce restenosis, intravascular radiation. This new technology has recently been applied in Europe and USA, and the first clinical studies have demonstrated its safety and feasibility with promising results on reduction of restenosis.

As a new technology emerges, new methodologies must be developed to assess its clinical impact. In chapter 6 we proposed a new QCA methodology, in which specific coronary segments were defined: target segment, injured segment, irradiated segment and vessel segment. Thus, we observed that "relocation" of the minimal lumen diameter is a frequent phenomenon following intracoronary radiation using the 90Y-source and should be considered when reporting the result of clinical trials.

Another fact to consider in the setting of radiation therapy is the need for accurate matching between the injured and irradiated zones. In the field of radio-oncology, the so-called geographic miss has been implicated in treatment failure. Thus, we investigated (chapter 7), using a specific QCA methodology, the incidence and clinical impact of not having completely covered the injured coronary segment by the radioactive source. Although we were dealing with a "benign" disease, geographical miss, which occurred in 31.9% of the cases, had also a negative clinical impact in our series, probably due to the combination of low dose radiation and vascular injury. Late lumen loss was much higher in the segments with geographical miss as compared to either irradiated or uninjured segments. The need for longer (> 30 mm) radioactive sources has become obvious, since one third of the cases of geographical miss would have been

avoided by the use of longer sources.

Considering the promising results of the first clinical trials (chapter 5) and based on the observations of the first part of this thesis, one may consider the possibility that intravascular radiation prevents both unfavorable vessel remodeling (after balloon angioplasty) and neointimal formation (after stenting). Therefore, in chapter 8, we assessed the effect of ^{32}P beta-radiation following coronary interventions with and without stents. By the use of IVUS-3D volumetric analysis, we demonstrated that radiation indeed reduces both unfavorable vascular remodeling in non-stented vessel and neointimal formation within stented segments. The results also suggested that plaque may grow outside the stent struts which was accommodated by vessel enlargement.

The fact that segments adjacent to the irradiated "zone" will invariably receive lower dose of radiation raises an important issue: "Does low-dose radiation induce lumen reduction and/or plaque growth in uninjured coronary segments?" Using IVUS-3D volumetric quantification (chapter 9), we observed that lumen loss and plaque proliferation were similar between low-dose irradiated and non-irradiated (non-injured) coronary segments. These results provide an encouraging answer to the above query. These findings together with those from chapter 6 highlight the need for precise matching of the injured and irradiated segments for clinical efficacy of intracoronary radiation.

Both catheter-based systems (high dose-rate) and radioactive stents (low dose-rate) have been used to deliver beta radiation in the clinical setting. Given the different dose rates and total dose delivered by each system, one may expect different arterial response subsequent to each treatment. Thus, we investigated (chapter 10), by the use of IVUS-3D volumetric analysis, the vascular response to either radioactive stent (0.75-1.5 μCi and 6-12 μCi) implantation or "conventional" stenting followed by catheter-based irradiation. Patients treated with conventional stents without radiation were also included in this study. The first observation that emerges from our analysis was that low-activity radioactive stents had a similar effect, in terms of neointimal formation, remodeling and "edge-effect", to that of conventional stenting without radiation. Secondly, we observed that both conventional stenting followed by irradiation and higher activity radioactive stents inhibits neointimal hyperplasia. The somewhat intriguing findings were the increase in total vessel and plaque volumes behind the stent when catheter-based irradiation was applied. This phenomenon, preliminarily described in chapter 7, was not observed after implantation of either conventional (without radiation) or radioactive stents. Finally, lumen loss at stent edges was comparable between groups.

After understanding the mechanisms and clinical applications of these new technology, a word of caution is provided in the final chapters (11-13) of this thesis, where potentially deleterious effects of intracoronary radiation were critically analyzed. In chapter 11, an alarming high (6.6%) incidence of sudden coronary occlusion late after intravascular radiation therapy was reported. Delayed endothelialization, late stent malapposition and persisting dissection may be implicated in this phenomenon. From this "unpleasant" experience, we learned that prolonged antiplatelet therapy is highly recommended after intracoronary radiation therapy.

Chapter 12 reports on the occurrence of stent malapposition detected by IVUS at 6-month follow-up, in spite of good apposition after the procedure. By volumetric IVUS-3D quantification we noticed that vessel significantly enlarged in the segment of stent malapposition. As described in the chapters 7 and 10, vessel enlargement (remodeling) is one of the major consequences of intracoronary radiation and may be observed even in the presence of coronary stents. The combination of rigid tubular stents, vessel enlargement and diminished tissue proliferation after radiation were the most plausible explanation for this uncommon finding. Considering that both stent malapposition and delayed reendothelialization may be implicated with late thrombosis and its potentially catastrophic consequences, implantation of

coronary stents in the setting of catheter-based radiation therapy may be discouraged.

The fact that residual dissections may not be resolved until 6 months after treatment in about 50% of the cases is another unique IVUS finding related to the use of brachytherapy (chapter 13). It is nevertheless important to note that the presence of unhealed dissection was not related with any untoward clinical consequences.

In conclusion, intracoronary radiotherapy is a robust and promising technique to prevent restenosis. Taking advantages of the accumulated knowledge in the first series of clinical trials, in which difficulties in dealing with the "unknown" became apparent, the second wave of clinical trials has the potential to establish the place of this new therapy. Whether this exciting technology is a panacea has not been defined yet, but it is not likely considering the adverse side-effects presented in this thesis. However, intracoronary radiation has certainly opened an avenue for the application of "new energies" in the field of interventional cardiology.

Samenvatting en Conclusies

Het mechanisme van restenose na percutane coronaire interventies and de behandeling hiervan is het onderwerp geweest van eerdere onderzoeken. De complexiteit en het multicausale van dit proces van restenose maakt dat het nog niet volledig begrepen wordt. Daarom is een eenduidige oplossing van dit probleem ook nog steeds niet gevonden. Het eerste deel van dit proefschrift behandeld het probleem van restenose na ballon angioplastiek en stent implantatie- de huidige standaard behandeling. In het tweede deel wordt een nieuwe behandelingsmethode om restenose te voorkomen beschreven: intracoronaire irradiatie. Specifieke biologische factoren (eerste hoofdstuk) en het gebruik van drie-dimensionele (3-D) intravasculaire echografie zijn de belangrijkste onderzoekstechnieken in dit proefschrift.

Deel 1

Hoofdstuk 1 geeft een overzicht van het complexe fenomeen restenose.
In hoofdstuk 2 wordt de relatie tussen de ontstekingsreactie, zoals geaktiveerde neutrofiele granulocyten die CD66 antigeen op hun oppervlak tonen, en de restenose na stenting en ballon angioplastiek onderzocht. Onze resultaten bevestigen de eerder geopperde positieve rol van geaktiveerde neutrofielen in het restenose proces na ballon angioplastiek. De afwezigheid van een positief effect van geaktiveerde neutrofielen op restenose na stenting zou op een rol van deze cellen in het proces van remodelering kunnen wijzen.
Hoofdstuk 3 bevestigt niet alleen het proces van negatieve remodelering na ballon angioplastiek, maar beschrijft bovendien de door ons geprefereerde methode van bestudering van restenose.Door gebruik te maken van deze nieuwe techniek: 3-D intravasculair ultrageluidsonderzoek waren we in staat om aan te tonen dat: 1. De uiting van remodelering verschilt tussen coronaire segmenten, 2. het coronaire segment dat het grootste verschil in lumen diameter toont bij vervolgonderzoek kan varieren.
In hoofdstuk 4 tonen we met 3-D echografische volume-metingen aan dat het restenose proces na implantatie van twee nieuwe stents berust op neointime vorming. Ondanks verschillen in ontwerp en draaddikte bleken Multi-Link- en NIR-stents, beide goedgekeurd door de FDA, allebei evenveel steun aan de vaatwand te verlenen over een periode van 6 maanden en aanleiding te geven tot een vergelijkbare hoeveelheid neointimale hyperplasie.

Deel 2

Hoofdstuk 5 beschrijft de klinische toepassing van een nieuwe therapie om restenose te voorkomen/behandelen: intravasculaire radiotherapie. Deze therapie werd recent voor het eerst toegepast in Europa and de USA, en deze eerste klinische studies toonden de toepasbaarheid, veiligheid en voorlopige effectiviteit bij de vermindering van restenose aan.
Wanneer nieuwe technieken het licht zien, hebben we vaak nieuwe methoden nodig om de effectiviteit te meten. In hoofdstuk 6 introduceren we een aangepaste methode voor quantitatieve coronair angiografie (QCA), waarbij specifieke coronaire segmenten worden gedefinieerd: het te behandelen segment, het door de (ballon)behandeling geraakte segment, het bestraalde segment en het behandelde bloedvat. Op deze manier konden we aantonen dat de plaats met de kleinste diameter (MLD) en dus de belangrijkste vernauwing vaak van plaats verschuift na intracoronaire bestraling met de Y-90 bron en dat dit fenomeen in aanmerking moet worden genomen bij de beschrijving van resultaten van klinisch onderzoek.

Uit het vorige volgt dat bij intravasculaire radiotherapie de bestraalde zone de behandelde zone nauwkeurig en volledig dient te omvatten. In geval dit niet gebeurd ontstaat er een situatie waarbij het doelgebied voor bestraling zogenaamd effectief geografisch wordt gemist, een bekende oorzaak van therapiefalen in de bestralingsbehandeling van tumoren. Daarom onderzochten we in hoofdstuk 7 met behulp van deze aangepaste QCA methode het voorkomen restenose in die gevallen waarin de radioactieve bron het behandelde coronaire segment niet voldoende had omvat. Het bleek dat in die gevallen de optredende weefselreactie inderdaad meer uitgesproken was en in veel gevallen (32%) aanleiding gaf tot klinische gevolgen. Late vermindering van de vatdiameter bleek significant vaker op te treden in de segmenten met geographisch gemiste bestraling, vergeleken met effectief bestraalde of onbeschadigde segmenten. Het gebruik van langere radioactieve bronnen zou een oplossing kunnen vormen voor dit fenomeen.

Restenose wordt voornamelijk veroorzaakt door vaatkrimp (na ballonangioplastiek) en neointimale hyperplasie (na stent plaatsing). Om het effect van radiotherapie te evalueren onderzochten we in hoofdstuk 8 het effect van P-32 beta radiatie op coronaire interventies met en zonder stents. Door middel van 3-D IVUS analyse konden we aantonen dat bestraling zowel negatieve remodelering na ballonangioplastiek als neointimale hyperplasie na stenting vermindert. De resultaten suggereren ook dat de groei van de atherosclerotische plaque buiten de stent toeneemt, maar dat dit gecompenseerd wordt door vergroting van de totale vaatdiameter.

Het feit dat vaatsegmenten aansluitend aan de bestraalde zone zonder uitzondering een lagere bestralingsdosis krijgt, werpt een belangrijke vraag op: "Stimuleert lage-dosering radiatie lumenafname en/of plaquegroei in onbeschadigde segmenten van de coronair arterie?" Met behulp van 3D-volumetrische ultrageluidsanalyse konden we in hoofdstuk 9 aantonen dat lumenafname en plaquegroei in vergelijkbare mate optraden in met lage dosis bestraalde en niet-bestraalde, niet bij PTCA beschadigde delen van de vaten. Deze bevindingen tezamen met die van hoofdstuk 6 benadrukken de noodzaak van precieze lokalisatie van de bestralingbron over het gehele beschadigde gebied om effectief te zijn.

Zowel lijnbronsystemen (hoge dosisafgifte per tijdseenheid), als radioactieve stents (lage dosis per tijdseenheid) worden toegepast tijdens klinisch onderzoek. Gegeven deze verschillen in stralingskwaliteit zou er een potentieel verschil in vaatwandreactie te verwachten zijn. Daarom vergeleken we in hoofdstuk 10 met 3-D volumetrische echoanalyse de vaatwandreaktie na een radioaktieve stent (0.75-1.5 μCi en 6-12 μCi) met die na een niet-radioactieve stent gevolgd door bestraling met een lijnbron. Als derde groep bestudeerden we patienten behandeld met een conventionele stent zonder bestraling. De eerste conclusie van ons onderzoek was dat radioactieve stents met de laagste aktiviteit zich niet anders gedroegen wat betreft neointimale groei, remodelering en "edge-effect", dan niet-radioaktieve stents.Ten tweede bleken conventionele stents die nabestraling ontvingen, en de hogere aktiviteit radioactieve stents beide neointimagroei te remmen. Tot onze verrassing namen we hierbij een toename van vaatvolume alsook plaquevolume waar, echter uitsluitend bij de groep met conventionele stents met nabestraling. Dus dit fenomeen van positieve remodelering dat als voorlopige resultaten gepresenteerd wordt in hoofdstuk 7, treffen we niet aan na radioaktieve stents, of conventionele stents zonder nabestraling.

Na het onderzoek naar de klinische toepasbaarheid en het werkingsmechanisme van deze nieuwe techniek, waarschuwen we in de hoofdstukken 11 tot 13 voor enkele potentieel nadelige bijwerkingen van intracoronaire bestraling. In hoofdstuk 11 rapporteren we als eersten een alarmerend frequent (6.6%) optreden van plotse late kransvatafsluiting na eerdere endovasculaire bestraling. Vertraagde endotheelcelbekleding, late stent-malappositie, en persisterende dissectie kunnen alledrie verantwoordelijk zijn geweest voor dit fenomeen. De les

van deze onaangename ontdekking was dat langdurige anti-thrombotische behandeling ten zeerste aanbevolen dient te worden na endovasculaire bestraling.

Hoofdstuk 12 beschrijft het vaststellen van stent "malappositie" (het overblijven van een ruimte tussen de stentdraad en de vaatwand) door IVUS na 6 maanden, ondanks een goede "appositie" (overal goed kontakt tussen stent en vaatwand) direct aan het eind van de implantatie. Met 3-D volumetrische intravasculaire echo konden we aantonen dat ter plaatse van de malappositie het bloedvat juist verwijd was. Zoals eerder beschreven in de hoofdstukken 7 en 10, is vaatvergroting (remodelering) een van de belangrijkste konsequenties van endovasculaire bestraling en treedt zelfs op in aanwezigheid van stents. Het samengaan van een rigide cylindrische stent, vaatvergroting en het verminderen van weefselgroei na radiatie vormt de meest plausibele verklaring voor deze bevinding. Overwegende dat zowel stent malappositie als vertraagde endotheelbedekking beide verantwoordelijk kunnen zijn voor late thrombotische afsluiting, en de meestal kwalijke gevolgen daarvan, dringt zich de gedachte op om terughoudend te zijn in het gebruik van stents in geval dat ook bestraling wordt toegepast.

Het feit dat vaatwand dissecties (scheuren) 6 maanden na de behandeling met radiatie nog in 50% van de gevallen niet genezen zijn, is een volgende echografische bevinding bij het gebruik van brachytherapie en beschreven in hoofdstuk 13. Het is in deze contekst echter wel belangrijk op te merken dat het persisteren van zo'n dissectie niet geassocieerd was met een late komplicatie.

Als eindconclusie van dit proefschrift mag gelden dat intracoronaire radiotherapie een krachtige en veelbelovende methode is om restenose te remmen. Gebruikmakend van de ervaring opgedaan tijdens de eerste klinische onderzoeken, kan verder klinisch onderzoek de plaats van deze therapie nader bepalen. Of deze interessante technologie als panacea kan worden toegepast, is nog niet uitgemaakt, maar gezien de bijwerkingen zoals geschetst in dit proefschrift niet waarschijnlijk. Intracoronaire radiotherapie vormt tenslotte wel duidelijk een nieuwe energiebron voor interventiecardiologen in hun strijd tegen restenose.

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I would first apologize to those nice people (in and out of the Thoraxcenter) that I could not get closer due to the restrained time and almost unreachable goal (this thesis) that I challenged myself, of course with the enjoyable "pushy" contribution of Prof. Serruys. Thus, it seems appropriate to remember some relaxing moments that I shared with the "fellow's family" from Thoraxcenter.

Starting by the famous argentinean fellow that does not need a "staged procedure" to swallow 1 Kg (1000 grams!) of meat, Dr Mariano Albertal. The first one to take me out of my apartment in a very dark and cold night in January. The place, of course, Locus Publicus.... I will never forget that he came with two beers and one Martini, but the Martini was not for my wife.... Dear Mariano, thank you for making "so frequent" and smart questions about "coronary flow", without them I would have missed several interesting concepts of coronary physiology.

Glenn van Langenhove, " Glenn-the-man" or "Glenn-tleman". Whatever name you give him sounds like a noble name. Dear Glenn, thank you for inviting us to play soccer on the beach in California - that was one of the magic moments I had abroad. Of course, you were smart enough to select a Japanese (Ken) and a Greek (Leo) to play on my side – we lost the game... Glenn also deserves a special acknowledgement for taking out of my mind the idea of performing interventions at the Thoraxcenter - instead, I was able to finish this thesis. Finally, I am not allowed to forget that he kindly let me (with my wife along!) live in his ("our") apartment during my last month in Rotterdam.

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Now let's talk about Jurgen Lighthart, the "permanent fellow". Dear Jurg, thank you very much for teaching me some "secrets" (at least for conventional IVUS analysts) of IVUS imaging. Thank you for being the "coach of the beer team" in several occasions.

Manel Sabaté, the starting point. Someone who deserves all my trust and friendship. It is not by coincidence that his name is quite often together with my name in most of the papers. I still remember that marvelous view (at 02:00 am!) from the top of the mountain in Barcelona – of course enjoying some beers, as we did several times to get inspiration for our research projects. Dear Catalan friend, life is quite different at home, instead of "waiting for the reviewers", we are both "waiting for our coming babies" – congratulations! Together with Pilar, Marta ("lovely and sacrificed" ladies) and Laura, I wish you all the best in "Spain"!

Ken Kozuma, the partner, the friend, the "brother". I will never forget how many sentences from manuscripts were re-written because of "Mr. Palmaz Schatz" - a friendly nickname due to his lack of flexibility in understanding some "far western" comments. I learned from Ken that silence may sometimes "sound" stronger than thousands of words - I am still improving on it... Dear Ken, in the end, I am sure that I became a more calm and reflective person and you became a bit "romantic"! The barbecue (with a lot of smoke!) at my apartment, together with the delicious dinners in your place really made my life less stressful in Holland. Many thanks to

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My co-promoter, Dr Willen J van der Giessen. Dear Wim, thank you very much for teaching me the true science. I am sure that without your always critical academic reviews this thesis would have never taken off. Talking about relaxing moments, that "happy hour" we had in Atlanta at the end of the AHA Congress serves as a good example.

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EDUCATION

1988 High School at Colégio Marista Dom Silvério, Belo Horizonte, Brazil

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1994 Research Fellowship at the Cleveland Clinic Foundation, Ohio, USA (Directors Jose Mauro Brum, MD and Paul A. Murray, PhD).

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1997-98 Fellowship in Interventional Cardiology at Felício Rocho Hospital (Director, Dr Jamil Abdala Saad), Belo Horizonte, Brazil.

1999 Fellowship at the Department of Intervention Cardiology at the Thoraxcenter, Heart Center Rotterdam, Erasmus University, Rotterdam, The Netherlands, (Chairman Prof. Patrick W. Serruys, MD, PhD).

ACADEMIC ACTIVITIES

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1993 Monitor of Pediatric Cardiology at the Medical School of the Federal University of Minas Gerais, Belo Horizonte, Brazil, (Director Prof. Cleonice C. C. Motta, MD, PhD).

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1997-98 Cardiologist Staff of the Intensive Care Unit at the Felício Rocho Hospital, Belo Horizonte, Brazil.

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