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Principles And Practice Of Vascular Brachytherapy

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TABLE OF CONTENTS

Foreword

In less than ten years vascular brachytherapy has exploded on the interventional cardiology and radiation oncology scenes as a major advance in the fight against post-angioplasty restenosis. This is especially encouraging given the dismal results of mechanical and pharmacological adjuncts in this setting. Several major clinical trials have been completed with the support from the industrial entrepreneurs, and the dedication and untiring efforts of pioneering clinicians and laboratory scientists. Based on the consistently positive results from these studies, vascular brachytherapy is now poised to enter the mainstream of clinical practice.

It is on this background that this new handbook is being offered to all the subspecialties that are involved in this multi-disciplinary effort. It presents a truly coherent compilation of the basic and clinical sciences of vascular brachytherapy, and will be of great value to anyone involved in the care of these patients.

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Preface

Cancer and vascular diseases are major causes of mortality and morbidity in the United States (accounting for well over 1.4 million deaths annually). Radiation therapy has an established role in the treatment of malignancies at all sites. Technological innovations and a better understanding of the oncologic processes have enabled us to optimize local control while minimizing undue toxicity. Brachytherapy has contributed considerably to this improved therapeutic ratio and is playing an increasing role in modern cancer therapy. Though brachytherapy is almost as old as the discovery of ionizing radiation, it was not widely used in this country due to the problems of radiation exposure and lack of accurate dosimetry. However, over the last four decades, better imaging techniques, advances in computer technology and physics, the development of new isotopes and the improvements in remote afterloading have all contributed to a virtual renaissance of brachytherapy in the United States.

Over about the same period of time, we have seen rapid advances in the management of cardiovascular and cerebrovascular diseases. Chief amongst these is the addition of percutaneous vascular recanalization in the armamentarium of physicians treating these potentially fatal conditions. It was only on June 16, 1964 that Dotter performed the first ever planned transluminal arterial dilatation. Within the next few years, percutaneous transluminal angioplasty (PTA) for coronary, peripheral and carotid arterial stenoses was well established as a minimally invasive approach to these disorders which were previously treated only with major surgery. Today, well over 700,000 coronary interventions are performed annually in the United States alone, at an estimated cost of 4 billion dollars. The initial enthusiasm for these techniques was soon tempered by the realization that the PTA often gave frustratingly temporary results. This problem of restenosis has proven to be surprisingly resistant to any simple solution despite over thirty years of research and clinical trials.

Today we are poised on the threshold of what promises to be a dramatic change in the way we look at vascular obstructions, and especially the problem of post-angioplasty restenoses. Altered local hemodynamics or the angioplasty injury are believed to set into motion a cascade of events culminating in a proliferative response, which, when *excessive and uncontrolled,* results in restenosis. The entire process is now considered more of a growth disorder and this has exciting implications for therapeutic interventions.

The growth inhibitory properties of ionizing radiation have been used for years to control benign proliferative disorders and this concept has been recently extended to the pathologic proliferative response following angioplasty. The effectiveness of radiation in this setting has now been shown quite consistently in laboratory animals, and the technique has been successfully employed in several large clinical trials. However, the location of most arteries precludes the use of external beam radiation due to the unacceptably high integral dose (and attendant toxicity). Brachytherapy, on the other hand, is optimally suited for the delivery of moderately high doses of radiation to the vessel walls. One of the earliest forms of "conformal radiation treatment", it allows for a very rapid fall-off of dose beyond the target volume, minimizing normal tissue toxicity. This has led to the development of endovascular brachytherapy.

Endovascular brachytherapy is a new and exciting field, which offers the promise of effective therapy for vascular restenosis. However, as with any new therapeutic modality, much work still needs to be done in the basic, clinical and technological arenas. In the eagerness to adopt what appears to be a highly effective therapy, it is important not to lose sight of the fact that little is known about its long-term effects, both in regards to durability of clinical results and patient safety.

One of the unique problems facing this new subspecialty is that, though it is a truly multidisciplinary endeavor, the specialists involved - interventional cardiologists and radiologists, radiation oncologists, medical physicists and radiation safety officers - have traditionally had very few occasions for interaction amongst themselves. Obviously, rapid progress in this field can only be made if there is a close working relationship, not only amongst the medical and physics teams but also the industry personnel. Unfortunately, the different specialties have their own unique "jargon" and they almost appear to be separated by a "common language".

This small handbook is not intended as a manual on "How To Do Endovascular Brachytherapy" (there is really no substitute for a formal hands-on training course prior to starting a new program). It is primarily designed to provide the different specialties with a glimpse of the other's world; if it succeeds in breaking the "language barrier" between the different disciplines, it will have achieved its goal.

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1

An Historical Perspective

"Those who cannot remember the past are condemned to repeat it."
- George Santayana.

The development of cardiac catheterization, angioplasty and other catheter-based interventions rank as some of the greatest achievements in cardiovascular medicine. Looking back in time, it is apparent that catheterization of hollow organs has been performed since antiquity. The Egyptians are known to have catheterized the bladder in 3000 BC using metal pipes (1), and the Greeks and Romans delivered rectal enemas using an animal bladder as a bag and a quill or metal tube as a catheter (2). However, it was only in 1665 that Wren performed the first intravenous injection in a dog. Two years later, Major followed this up with the first intravenous injection in a human in 1667. The first recorded cardiac catheterization was performed in 1711, when Reverend Hales inserted brass pipes into the ventricles of a horse via the jugular and carotid routes (3). Despite this, more than a hundred years would pass before the actual term "cardiac catheterization" was coined by Claude Bernard in 1844. Bernard was also the first to accurately record the intracardiac pressures, and describe right- and left-heart catheterization via the femoral routes, along with the sampling of blood at various points in the arterial and venous systems (4). Following the discovery of X-rays by Roentgen, on November 8, 1895, the field advanced very rapidly. In 1919, Heuser documented the first angiogram in a living person by injecting potassium iodide into the hand veins and observing the forearm veins with a fluoroscope (5). Shortly thereafter, Brooks used sodium iodide to obtain the first arteriograms in living humans (6).

Less than 5 years following this, in July 1929, Werner Forssmann performed the first successful catheterization of the right heart in humans. Fresh out of medical school, at the age of 25 years, he became interested in the safe delivery of intracardiac medications to victims of cardiac arrest. After using ureteral catheters to successfully catheterize the right heart in cadavers, Forssmann convinced a colleague to pass a catheter into his right basilic vein via a percutaneous approach. Midway during the experiment, his colleague panicked and pulled the catheter out. Forssmann's superiors got wind of this and prohibited him from doing any further experimentation. Undeterred, he gained the trust of a surgical nurse, Gerda Ditzen, to access the necessary venesection instruments. As he described it in his autobiography (7, 8, 9):

I ..... decided to go ahead with the experiment on my own heart, secretly and quickly. But I needed an assistant, the surgical nurse. I had to win her over or I would have no access to the necessary sterile instruments.

I let a few days go by and then started to prowl around Nurse Gerda Ditzen like a sweet-toothed cat around the cream jug. I knew I'd be able to carry out my black deed only during afternoon siesta while everyone in the hospital was dozing, so I made it a point of dawdling in the canteen after lunch, hoping to meet Nurse Gerda as she left the nurses' dining room. We often lent each other books, so it was easy to find something to gossip about; and she'd invite me back to her little office next to the operating room for a cup of coffee ..... When, about a fortnight after my conversation with Schneider, she said with a sigh, "What a pity we can't do the experiment together !" I decided the time had come.

The following afternoon the good lady was sitting in her cubicle when I breezed in, whistling cheerfully. "Nurse Gerda, I want you to give me a set of instruments for a venesection under local anesthesia, and a ureteral catheter."

She started up suspiciously. "But no one in the ward's scheduled for a venesection. You're not planning to do that experiment of yours against the boss's orders are you?"

"Nurse Gerda, you need to know nothing about what I am going to do. But supposing I were to do the experiment - it'd be quite safe."

She eyed me closely. "Are you absolutely sure there's no danger?'

"Absolutely"

"All right then, do it to me. I put myself in your hands."

"Well, why not? You'll be the first person in history to undergo such an experiment."

Of course, I had no intention of going through with this, but it was the only way to get the instruments. She got everything ready in the little operating room, then sat down and held out her left arm. When I suggested she lie down on the operating table she flatly refused at first. But I reminded her how, as she knew from her own experience, patients sometimes collapse from even the smallest doses of novocaine, and so I preferred her to be lying down for the anesthetic. She gave in, and with the speed of light I strapped her legs down so tightly that she could not reach the buckle; I then tied down her hand. Amazingly enough she accepted my explanation ..... In a twinkling of an eye I had anesthetized my left elbow. Now I went back to her and began to iodize her left elbow ceremoniously, and then to lay a sterile cloth over it, all very slowly and deliberately in order to kill time. When my anesthetic began to take effect I quickly made an incision in my skin, inserted a Deschamps aneurysm needle under the vein, opened it and pushed the catheter about a foot inside. I packed it with gauze and laid a sterile split over it. Then I released Nurse Gerda's right hand and loosened the straps around her knees.

"There we are, it's ready now. Please call the x-ray nurse."

Only then did she realize what had happened. She started to yell at me for having deceived her. It wasn't far to the x-ray room, but we had to go down into the basement, and by the time we arrived, Nurse Eva was waiting for us. Upon my instruction she placed me behind the fluoroscope screen.

News spread like wildfire in a hospital. Suddenly Romeis burst in, half asleep and his hair all tousled: "You idiot, what the hell are you doing?" He was so desperate he almost tried to pull the catheter out of my arm. I had to give him a few kicks in the shin to calm him down.

Forssmann was immediately fired by his superiors, but went on to win the Nobel Prize in 1956, along with fellow catheterization pioneers, Cournand and Richards. By the 1940s, right-

heart catheterization, and its use in pressure recording, oximetry and angiography, had become so advanced that the technique is little different today, except for the use of balloon-tipped catheters and a variety of different catheter materials.

Retrograde left-heart catheterization was performed in animals by several early pioneers. However, because of concerns regarding crossing the aortic valve, several crude, risky and daring methods involving direct antegrade punctures were developed for advancing catheters into the human left ventricle or left atrium. It was only in 1950 - almost 20 years after the first successful right heart catheterization - that successful human retrograde left-heart catheterizations were first reported independently by Zimmermann et al (10) and Limon-Lason et al (11).

The stage was finally set for selective coronary angiography. At the Cleveland Clinic, Sones had noticed the nonselective coronary opacification during ventriculography and aortography in children in 1958. He began experimenting by performing semi-selective coronary angiography in dogs, placing the aortic catheter in either of the coronary sinuses of Valsava, in order to inject the contrast closer to - but not into - the coronary ostia. On October 30, 1958, serendipity intervened (12). In Sones' own words,

" ..... we performed a left ventriculogram on a patient with an acquired valve disease. I was working in the hole beneath the table in order to observe the image amplifier screen during the injection. I asked my associate to withdraw the catheter tip across the aortic valve to the ascending aorta. My associate complied and we relied on the pressure change from the left ventricle to the ascending aorta without .... confirming the exact location of the tip ..... My associate, Dr. Royston Lewis, made an injection of 40 cc of 90% Hypaque through the catheter. About one second before the injection was initiated, I hit the switch to initiate a cine run. When the injection began, I was horrified to see the right coronary artery become heavily opacified and realized the catheter tip was actually inside the orifice of the dominant right coronary artery. I shouted, "Pull it out." Our combined reaction times to accomplish withdrawal of the catheter consumed 3 - 4 seconds, which meant that approximately 30 cc of the 90% Hypaque had been delivered into the right coronary artery. I was of course horrified because I was certain that the patient would develop ventricular fibrillation ..... .

He grabbed a scalpel with the intent of performing open-massage. Instead of ventricular fibrillation, the patient developed asystole. The patient was still conscious and was resuscitated via coughing, and went on to make a complete recovery. Sones soon developed the new technique of selective coronary angiography with specially formed catheters. In 1962, Ricketts and Abrams (13) introduced new preformed polyethylene catheters and a percutaneous femoral artery approach. These catheters and the femoral approach were refined further by the efforts of Judkins of the University of Oregon and Amplatz of the University of Minnesota (14, 15).

History of Catheter Angioplasty

The origin of transluminal angioplasty is attributed to Dotter, who not only pioneered the technique, but also coined the name for the procedure. As is often the case, the procedure was first performed inadvertently during a routine angiography on a patient with atherosclerosis (16, 17):

..... In one patient, despite a somewhat weak pulse at the site of entry, the femoral artery was entered and a spring-guided catheter passed without difficulty to the distal aorta. Removal of the guide and injection of the contrast material revealed that the catheter had been inadvertently passed through a completely occluded iliac lumen.

With the thought that one patient's "complication" might lead to another's therapy, cadaver studies were done in order to explore the feasibility of deliberately using catheters to effect favorable modifications in the locally inadequate arterial lumen.

On Jan. 16, 1964, the first intentional transluminal dilatation was done in an 82 year old woman who presented with a cold, painful, pulseless left leg with an ischemic ulcer and gangrene of three toes, due to a high grade, localized 0.5 cm stenosis of the adductor hiatus with distal vascular disease. She was not thought to be a candidate for vascular reconstruction, and refused amputation. Dotter therefore attempted a dilatation, passing a guide through the stenosis and dilating it with coaxial polyethylene catheters. The entire procedure took only 20 minutes, and distal pulses were immediately noted. The skin and ulcers healed, and after the gangrenous toes sloughed off, the patient was able to walk for the first time in 6 months; she remained ambulatory till her death 3 months later from congestive heart failure.

Encouraged by this initial success, Dotter and Judkins described a total of 15 procedures in 9 patients. All patients had severe symptoms, and most were rejected for revascularization. The initial results were impressive - 4 amputations were avoided, and 6 out of 9 patients improved. They found that the procedure was most successful for short stenoses and that poorer results were obtained for blockages involving long segments. They appreciated the great potential of the technique for the treatment of peripheral vascular disease and also, as they stated,

" ... severe proximal narrowing of the coronary artery will be amenable to a manually guided dilator inserted via an aortotomy or via the brachial artery ..... ".

These ideas met with much skepticism, especially from surgical colleagues on whose territorial right they were encroaching. For example, Dotter received a requisition from a surgical colleague for a left femoral angiogram: the form stated "Visualize but do not try to fix !!!!!" Dotter dutifully left the lesion in that artery alone, but could not help successfully dilating the one in the contralateral artery. Others also found it difficult to believe that a hard, calcified plaque could actually be dilated without untoward sequelae. The need to introduce large bore rigid dilators percutaneously and then apply large shear forces with the dilators made the technique crude and risky. In addition, the "snow-plow effect" jeopardized branch vessels. Thus, over the next decade, there was little enthusiasm for catheter dilatation in the United States. The technique was, however, increasingly applied in Europe, and several modifications in the Dotter coaxial catheter were introduced - Staple and Van Andel used tapered catheters, and side holes were added by Zeitler. Stenosis of the iliac, femoral and popliteal arteries were dilated with an initial success in two thirds of the patients and lasting benefits in over half of the small number of patients who had a long-term follow up.

Evolution of Balloon Angioplasty (16)

Arnott, in 1819, was the first to use a balloon to dilate a urethral stricture. This was followed by the development of balloon esophageal dilatation by Plummer in 1906, and the latex balloon catheter by Foley in 1932. In 1964, Dotter and Judkins recognized the need for a catheter

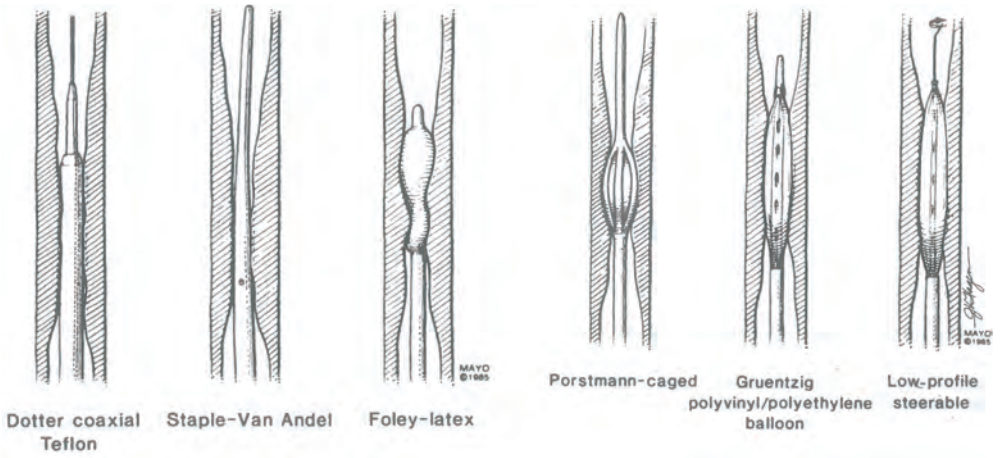

Figure 1.1 : Evolution of balloon angioplasty catheters. From: Shepard RFJ, Vilestra RE: The history of balloon angioplasty. In: Vilestra RE, Holmes DR (eds.): PTCA: Percutaneous Transluminal Coronary Angioplasty. Philadelphia: FA Davis, 1987. Reproduced with the permission of the Mayo Foundation

"capable of externally controlled concentric expansion over a suitable portion of its length". Initially, latex balloons were tried, but they proved ineffective because they were compressible and would dilate in the direction of least resistance in the form of an hourglass. Porstmann, in 1973, produced a solution to this problem in the form of a caged or "Korsett" balloon catheter, consisting of a latex balloon surrounded by a catheter with struts to form a cage (Fig. 1.1). In 1974, Gruentzig first introduced the forerunner of the modem balloon catheter. It was constructed of polyvinyl chloride, which had the advantages of producing a rigid balloon that inflated to a pre-determined diameter (4 - 8 mrn) and of producing a large radial force with 3 to 5 atmospheres of pressure. He refined this concept into a double-lumen catheter fitted with a nonelastic polyvinyl chloride balloon and used it for human peripheral arterial angioplasty. Against the backdrop of current medical practice, it is incredible to note that Gruentzig actually fabricated all his catheters at nights or on weekends in his kitchen until 1976, when the Schneider and Cook companies took over the production. Following a successful outcome with the use of the balloon catheter in the leg arteries, the use of the balloon catheter was rapidly extended to other vascular sites and conditions, including renal, basilar, celiac and subclavian arteries, aortic coarctation, pulmonary artery stenoses, and valvular stenoses.

The evolution from peripheral vascular balloon angioplasty to dilatation of the coronary arteries was cautious (and justifiably so), because of the concerns regarding acute coronary artery occlusion and myocardial infarction. In May 1977, at St. Mary's Hospital in San Francisco, Gruentzig and Myler performed the first human coronary angioplasty *intraoperatively* during

bypass surgery. The angioplasty was performed by passage of the balloon catheter in a retrograde fashion through an arteriotomy in the native LAD artery distal to the stenosis (before placement of the bypass graft). By August 1975, they had performed the procedure on 15 other patients. The next big advance was made on Sept. 16, 1977, when Gruentzig performed the first successful *percutaneous* transluminal coronary angioplasty on a 38 year-old insurance salesman with 85% narrowing of the left anterior descending coronary artery. According to Gruentzig's account (12):

" ..... The patient was informed about the availability of balloon angioplasty in his case. The idea of preventing coronary bypass surgery was appealing to him inspite of the fact that he was informed of his being the first patient ever treated with this technique. He enthusiastically gave his consent and the catheterization laboratory at the University Hospital in Zurich, Switzerland, was set up for the procedure on September 16, 1977. (Employing a Seldinger approach through the right groin) ..... The guiding catheter was placed in the left coronary orifice and the dilatation catheter was inserted. Both catheters were connected to the pressure lines. The left femoral artery was also punctured and a sheath was placed. This was done to have arterial blood available to pump via a roller pump through the main lumen of the dilatation catheter into the coronary artery to perfuse the myocardium during balloon inflation .

..... The dilatation catheter was advanced to the stenosis with no difficulty. The stenosis was severe, but the catheter slipped through it without resistance. The catheter wedged the stenosis so that there was no antegrade flow and the distal coronary pressure was very low. To the surprise of all of us, no ST-elevation, ventricular fibrillation or even an extrasystole occurred and the patient had no chest pain. After the first balloon deflation, the distal coronary pressure rose quite nicely. Encouraged by this positive response, I inflated the balloon a second time to relieve the residual gradient. Again the patient had no chest pain. After balloon deflation, the distal coronary blood pressure normalized as compared to the aortic pressure indicating a good relief of stenosis ..... "

By January 1979, Gruentzig had done more than 50 coronary dilatations with a success rate of 60%. The technique has subsequently spread worldwide with several refinements and improvements in instrumentation and techniques.

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2

The Normal Artery & Basic Coronary Anatomy

Arteries are not simply a passive system of tubes of uniform and fixed Composition that distribute blood to the organs. The major arteries are complex biomechanical structures that carry out a wide array of mechanical and metabolic functions under a range of conditions. The arterial wall consists of three concentric layers or zones. From the lumen outwards, these are the intima, the media and the adventitia (Fig. 2.1).

Intima

The intima extends from the luminal endothelial lining to the internal elastic lamina. It consists of the endothelium with a coating of glycocalyx on the luminal aspect, the basal lamina, the subendothelial connective tissue, and the internal elastic lamina.

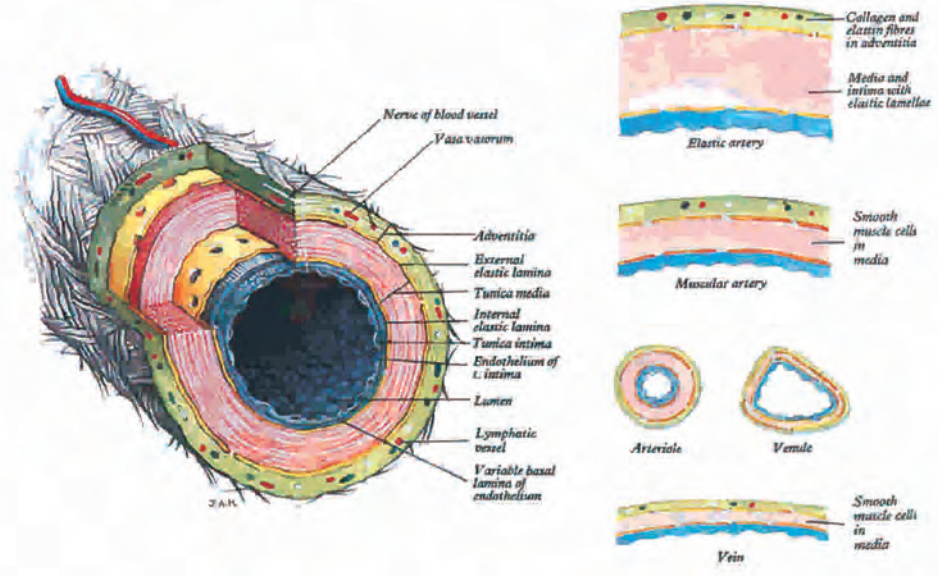

Figure 2.1 : Structure Of Medium Sized Muscular Artery. Reprinted from "Chapter 10 - Cardiovascular System". In: Williams PL (ed). Gray's Anatomy, 38th ed New York, Churchill Livingstone, 1996. With permission.

The endothelium is composed of a continuous monolayer of flat, polygonal cells, which tend to be aligned in the direction of the blood flow. The edges of adjacent endothelial cells

overlap, with the downstream edges of most endothelial cells overriding their immediate downstream neighbors, much like shingles on a roof. Changes in cell shape and in the extent of junctional overlap among adjacent endothelial cells occur in relation to changes in artery diameter associated with pulsatile blood flow, in relation to changes in configuration associated with bending or stretching, and in relation to the intimal accumulation of cells and matrix fibers during the development of intimal atherosclerotic plaques. These changes act to prevent the development of endothelial discontinuities. A protein layer called the glycocalyx coats the luminal surface of the endothelium.

Immediately deep to the endothelial layer is a closely associated fibrillar layer called the basal lamina. This structure is thought to form a continuous bond between the endothelial cells and the subendothelial connective tissue matrix. Numerous focal attachments are also present between the endothelial cells and the underlying intemal elastic lamina. The extensive basal lamina provides a supple, pliable junction well adapted to permit bending and changes in diameter or configuration associated with the pulse pressure without disruption or detachment of the endothelium. The focal, tight, relatively rigid junctions may prevent downstream slippage or telescoping, which could result from shear stresses imposed by blood flow. The basal lamina is composed of a unique type of collagen (Type IV) in association with two structural glycoproteins, laminin and entactin, while heparan sulfate forms the main proteoglycan. The type IV collagen supplies mechanical support and forms the scaffold of the basement membrane to which the other constituents are attached. Laminin is a glycoprotein involved in cell attachment; it also forms stable complexes with entactin, and can bind to heparan sulfates as well as heparin. Heparan sulfate proteoglycans are strongly negatively charged and control filtration through the basement membrane.

The *sub-endothelial connective tissue* lies between the basal lamina and the *internal elastic* lamina. It consists mainly of connective tissue fibers, with a few scattered macrophages and smooth muscle cells. Mast cells are also found in substantial numbers. Each mast cell contains about 20 μg of heparin (which is normally stored in its metachromatic granules).

The endothelial layer is considered to function as a thrombosis-resistant surface as well as a selective interface for diffusion, convection and active transport of circulating substances into the underlying arterial wall. Endothelial cells are now known to be metabolically active cells that play a very important dynamic role at the blood-vascular wall interface by regulating several processes including coagulation, fibrinolysis, platelet aggregation, leukocyte adhesion and cell migration.

The endothelial cells produce Factor VIII and V, and have a procoagulant activity. In response to vascular injury, they also secrete von Willebrand factor, which promotes platelet adhesion to the exposed subendothelial matrix. On the other hand, they secrete prostacyclin, which is a very potent inhibitor of platelet aggregation. Similarly, endothelial cells have a surface receptor, thrombomodulin, that, in the presence of thrombin, actives protein C. This protein C has anticoagulant activity by inactivating Factors VIII and V. Endothelial cells also secrete protein S, another powerful anticoagulant. In addition, anticoagulant activity is expressed by binding of thrombin to antithrombin-III, which in tum is complexed with the heparin-like glycosaminoglycans of the endothelial cell membrane.

Endothelial cells play a prominent role in fibrinolysis. They release several forms of plasminogen activators, including a urokinase-like and a tissue-type plasminogen activator.

Paradoxically, they are also involved in the production of plasminogen activator inhibitors (PAl), which can inhibit the activity of plasminogen activators. PAl binds to extracellular matrix produced by the endothelial cells; this may stabilize the PAl against spontaneous loss of activity. Activated protein C is also known to stimulate the fibrinolytic activity of the endothelial cells, while diminishing the anti-activator activity.

It is obvious that, in the natural state, the endothelial cells exert a very delicate, and yet precise array of checks and balances which determine the final thrombotic-fibrinolytic state. Furthermore, by direct intercellular communications, and by the release of autocrine and paracrine growth factors, endothelial cells also have the potential to modulate the smooth muscle cell function within the vessel wall. *The unexpected complication of late stent thrombosis, following endovascular brachytherapy, may well be a consequence of radiation-induced endothelial cell damage, with consequent disorganization of this delicate system in favor of a thrombotic/anti-fibrinolytic state.*

Media

The media extends from the internal elastic lamina to the adventitia. Although an external elastic lamina demarcates the media from the adventitia, in many vessels the external elastic lamina may not be distinct. The main components of the media are the smooth muscle cells in close association with elastin & collagen fibers (Fig. 2.2).

The *smooth muscle cell layers* are composed of groups of similarly oriented cells, each surrounded by a common basal lamina and a closely associated interlacing basketwork of Type III *collagen fibrils* which tighten around the cell groups as the media is brought under tension. This configuration prevents excessive stretching or slippage. The collagen fiber bundles also provide much of the tensile strength of the media, limit distention & prevent disruption. In addition, each cellular subgroup or fascicle is encompassed by a system of similarly oriented *elastic fibers,* such that the effective unit of structure is a musculoelastic fascicle. The elastic fibers are relatively extensible and allow for some degree of compliance; they recoil during the cardiac cycle and tend to distribute mural tensile stresses uniformly. The smooth muscle cells also produce the matrix which consists of a variety of proteoglycans, including heparan sulfate, chondroitin sulfate and dermatan sulfate. Smaller muscular arteries contain relatively less collagen and elastin and more smooth muscle cells than the aorta and the larger elastic arteries. Also, the muscular arteries contain a relatively higher proportion of collagen and a lesser amount of elastin, while the reverse is true for the larger vessels.

The normal function of the smooth muscle cell is to maintain vascular tone, and it does this via the actin and myosin filaments, along with the actin-associated proteins (actinin, filamin and tropomyosin). They also synthesize the collagen and elastin fibers, and other connective tissue elements such as the glycosaminoglycans, fibronectin and thrombospondin. Besides this, they are actively engaged in metabolic processes that may contribute to wall tone, and may be related to susceptibility to plaque formation. Thus, under conditions of increased pulse pressure, increased wall motion, and increased wall tension, medial smooth muscle cell metabolism is increased as is plaque formation. The reverse is observed when wall motion & pulse pressure are decreased (even in the face of strong atherogenic stimuli like marked hyerlipidemia !).

Apart from the various neural and humoral signals, vessel wall contractility is also regulated by local mechanisms. Endothelial cells release prostacyclin and the endothelium-derived

relaxing factor, now known to be nitrous oxide. These act via the cAMP and cGMP systems respectively, and not only regulate the vascular tone, but also regulate the platelet-vessel wall interaction. There are other, endothelium-independent, vasodilators like atrial natriuretic factor (ANF), etc.

Endothelial cells also influence vasoconstriction by the release of the very potent endothelin. In addition, norepinephrine, thrombin, neuropeptide Y, hypoxia, stretch and increased intramural pressure all cause vasoconstriction that is dependent upon, or enhanced by, an intact endothelium. Atherosclerotic arteries may exhibit impaired endothelium-dependent relaxation, while retaining the ability for endothelium-dependent contraction - this favors the occurrence of vasospasm and local thrombosis. *In a similar fashion, the endothelial injury by the angioplasty procedure, compounded by the effect of ionizing radiation on the remaining endothelial cells, may alter this delicate balance in favor of vasospasm and thrombosis.*

In response to injury, the smooth muscle cells show a phenotypic modulation from a resting, quiescent, contractile state to a synthetic, secretory, proliferative and migratory state. Macrophages can stimulate this phenotypic switch in cell cultures. One proposed mechanism involves the release of an endoglycosidase that degrades the heparan sulfate in the basement membrane of the smooth muscle cell. Besides macrophages, platelets and T-Iymphocytes are other sources of endoglycosidase. These macrophages and lymphocytes are very radio-sensitive; inactivation of this pathway could provide a potential mechanism by which relatively modest doses of radiation result in durable inhibition of neointimal hyperplasia.

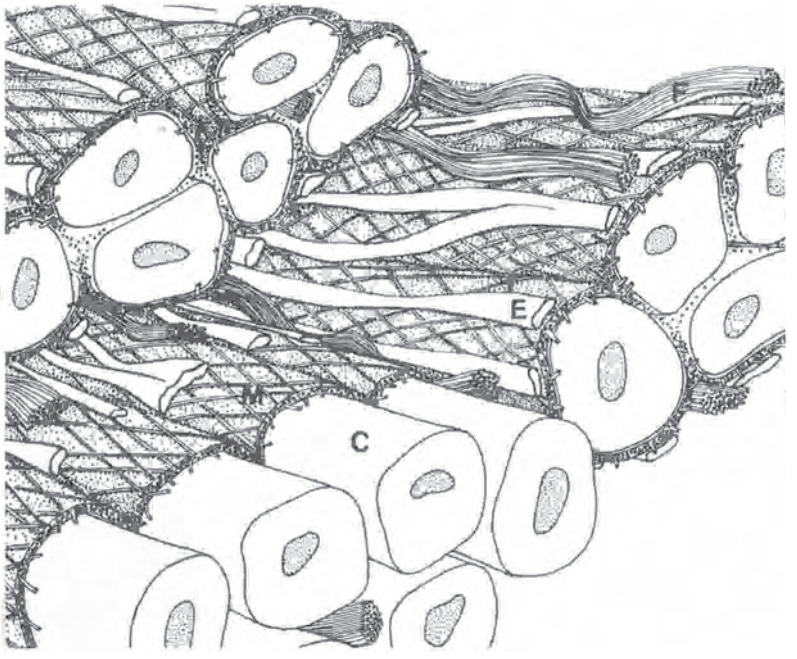

Figure 2.2: Diagrammatic representation of microarchitecture of the wall of a muscular artery. The long axes of the smooth muscle cells (C) of the media are oriented axially or perpendicular to the long axis of the artery. Cells are surrounded by a matrix (M) of basal lamina and collagen fibrils. Elastic fibrils (E) are less prominent. Collagen bundles (F) are interspersed. From Clark JM, Glasgov S. Transmural organization of the arterial media. Arteriosclerosis 1985;5:19-34; With permission of Lippincott, Williams & Wilkins.

Adventitia

The boundary between the adventitia and the media is usually distinct, even in the absence of a well-defined external elastic lamina. However, the outer limit of the adventitia may be difficult to identify, for it is often contiguous with the surrounding perivascular connective tissues. When compared to the media, the adventitia is quite acellular; only a few fibroblasts, adipocytes and an occasional mast cell are normally present. The adventitial matrix contains lipids, structural glycoproteins, and glycosaminoglycans, besides elastic and collagen (mainly Type I and III) fibers. Removal of the adventitia has little effect on the static pressure-volume relationships in elastic vessels like the aorta. In the muscular arteries, the adventitia may be more important because connective tissue fibers are relatively sparse in the media, and a thick, structured adventitia serves to provide significant tethering and axial tensile strength, prevent excessive dilatation and dampen the cyclic changes in tangential tension associated with the pulse pressure wave. In situations where a large intimal, atherosclerotic plaque overlies an atrophic media, the thickened adventitia may be the principal mural structural component of the artery wall.

Vasa Vasorum

The inner layers of the artery are nourished by diffusion of nutrients from the lumen. Diffusion is probably sufficient for the inner 0.5 mm of the media, which corresponds to about 30 medial fibrocellular lamellar units. When the arterial wall is thicker than this, the outer layers of the media are nourished by the vasa vasorum. Vasa vasorum arise from the parent artery, arborize in the adventitia and nourish the outer media. Intimal plaques may prevent diffusion from the lumen; this may provide a hypoxic angiogenetic stimulus, resulting in a greater in-growth of vasa vasorum. However, in thick walled arteries, the wall stresses and deformations may adversely affect the blood flow through the vasa vasorum. These changes in the vascular supply of the arterial wall and the plaque may eventually set the scene for intraplaque hemorrhage and subsequent plaque rupture. *Post-PTCA injury to the vasa vasorum is also believed to play a role in stimulating adventitial myofibroblasts and thus contributing to neointimal hyperplasia. In vascular brachytherapy, there has been some concern that the use of centering balloons may compress the vasa vasorum and cause medial hypoxia; this could potentially reduce the radiosensitivity of the target cells in the media.*

Basic Coronary Anatomy

The heart is supplied by the right and the left coronary arteries, each of which originates in the corresponding aortic sinus.

The main coronary trunks can be considered to lie in one of two orthogonal planes (Fig. 2.3). The anterior descending and posterior descending arteries lie in the plane of the interventricular septum and the right and circumflex coronary trunks lie in the plane of the atrioventricular valves. In the 60° left anterior oblique (LAO) projection, one is looking down the plane of the interventricular septum, with the plane of the atrioventricular valves seen en face; in the 30° right anterior oblique (RAO) view, one is looking down the plane of the AV valves, with the plane of the interventricular septum seen en face (Fig. 2.4).

To better characterize the arterial anatomy, the X-ray tube is often given a cranial or a caudal angulation (Fig. 2.5).

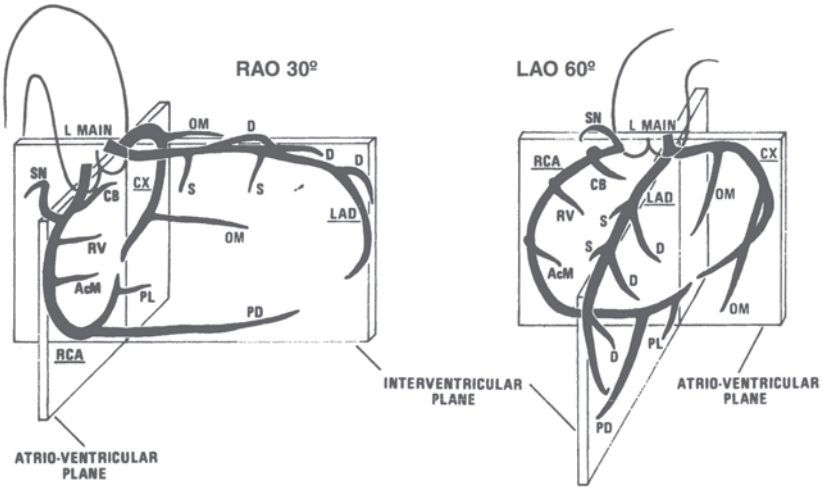

Figure 2.3: Representation of coronary anatomy relative to the interventricular septum and the atrioventricular valve planes. Coronary branches are as indicated - L Main (left main), LAD (left anterior descending), D (diagonal), S (septal), CX (circumflex), RCA (right coronary), CB (conus branch), SN (sinus node), AcM (acute marginal), PD (posterior descending), PL (posterolateral left ventricular). From: Baim DS, Grosman W: Coronary Angiography. In: Baim DS, Grossman W (eds) Cardiac Catheterization, Angiography and Intervention, 5th Ed. Baltimore, Williams and Wilkins, 1996. With permission.

Left Coronary Artery

The proximal left main coronary artery continues for a variable distance before dividing into its anterior descending (LAD) and circumflex (Cx) branches. Occasionally it may trifurcate with an intermediate branch bisecting the angle between the LAD and the Cx. The LAD originates at

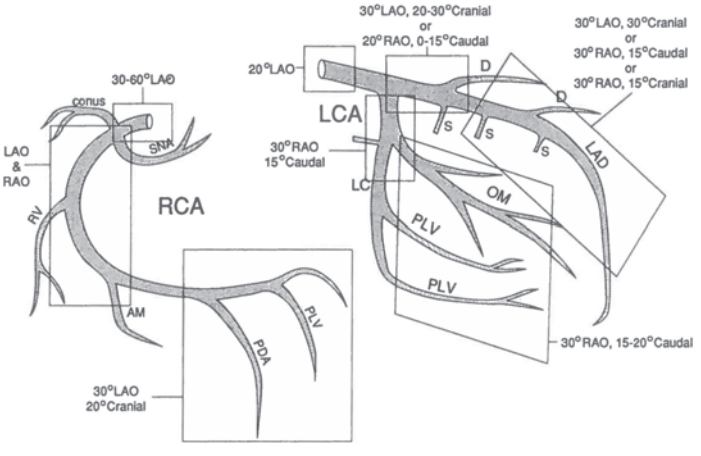

Figure 2.4: Schematic representation of the right (RCA) and left (LCA) coronary arteries depicted in the left anterior oblique (LAO) and right anterior oblique (RAO) projections respectively. Appropriate frontal and saggital plane projections and angulations for visualization of the various portions of the coronary arteries are indicated .. From: Pepine CJ, Lambert CR, Hill JA: Coronary Angiography. In: Pepine CJ, Hill JA, Lambert CR (eds). Diagnostic and Therapeutic Cardiac Catheterization, 3rd ed. Baltimore, Williams and Wilkins, 1998. With Permission

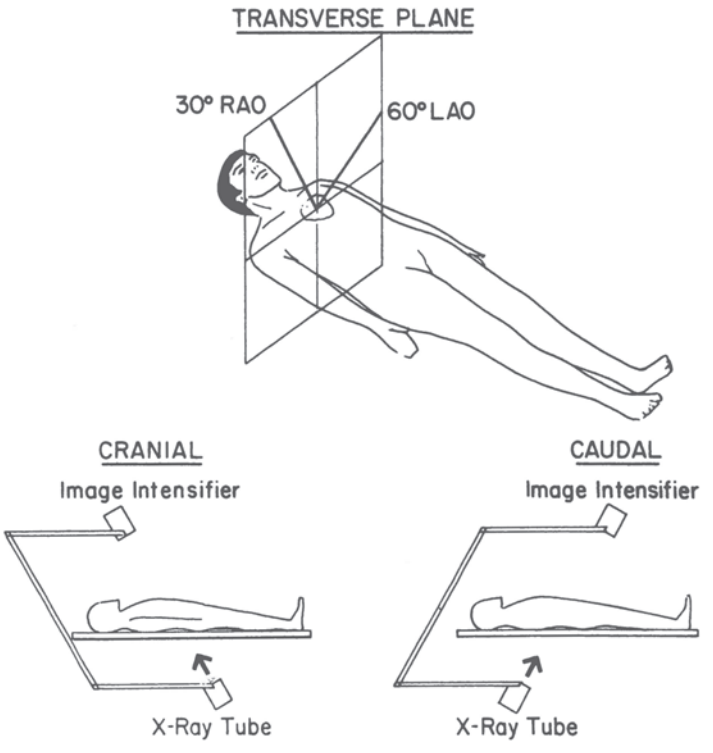

Figure 2.5: Illustration of the common angulations of the X-ray tube that are employed during coronary angiography and interventions. Bairn DS, Grosman W: Coronary Angiography. In: Baim DS, Grossman W (eds) Cardiac Catheterization, Angiography and Intervention, 5th Ed. Baltimore, Williams and Wilkins, 1996. With permission.

an obtuse angle from the left main and courses anteriorly, inferiorly and towards the patient's right to descend in the interventricular groove to the apex of the heart. It gives off the septal and the diagonal branches. The septal branches arise at right angles and are an important clue to identifying the LAD on an angiogram; they deeply penetrate and supply the interventricular septum. They vary in number, and the first branch is often large enough to warrant angioplasty or bypass considerations. The diagonal branches arise at obtuse angles to the LAD and descend diagonally to the obtuse margin of the heart. The diagonal branches vary in number and size, but usually the first 2 - 3 branches are large enough to be considered for angioplasty or bypass. The first diagonal branch serves as the boundary between the proximal and mid portion of the LAD. Thus, the portion of the artery prior to the origin of the first diagonal is known as the proximal LAD, while the segment just beyond the first diagonal is the mid LAD. The segment beginning halfway between the first diagonal and the end of the LAD is called the distal segment.

The circumflex (Cx) continues in the same general direction as the left main coronary to enter the left AV groove; it moves away from the LAD and wraps around to the back of the heart. It gives off the obtuse marginal branches (OM) in its proximal or initial portion. As it makes its way to the posterior portion of the heart, it gives off one or more left postero-Iateral (PL) branches. In 85% of cases, the Cx ends here and is called a non-dominant system. In the other 15% of the population, the Cx is "dominant" and supplies a left posterior descending coronary artery (PDA), which travels in the posterior interventricular groove. (Figs. 2.6, 2.7).

The Right Coronary Artery

The right coronary artery (RCA) descends to the patient's right in the anterior right atrioventricular groove. It often gives off a conus branch to the right ventricular outflow (as its fIrst branch) and then gives off 2 - 3 right ventricular branches. An SA Nodal branch encircles the SVC and there is usually a major acute marginal branch (AcM). It terminates by dividing into the

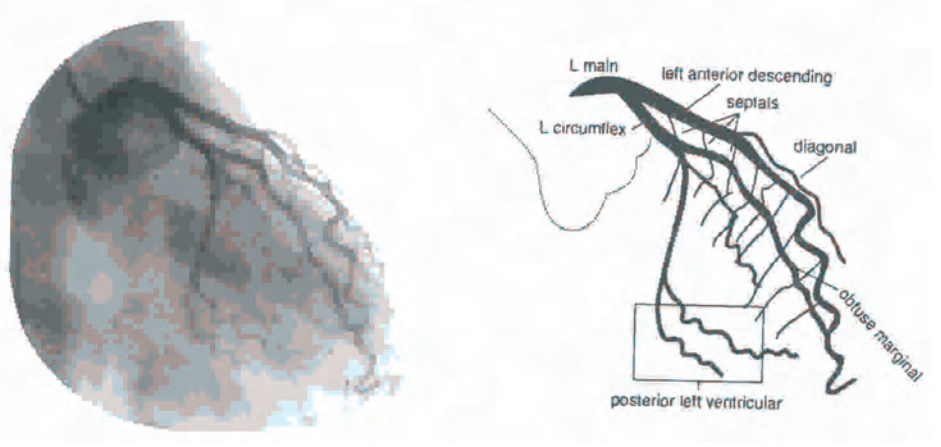

Figure 2.6: Normal radiographic anatomy of the LCA and its branches as seen in the right anterior oblique projection with a 15 degrees caudal angulation. From: Pepine CJ, Lambert CR, Hill JA: Coronary Angiography. In: Pepine CJ, Hill JA, Lambert CR (eds). Diagnostic and Therapeutic Cardiac Catheterization, 3rd ed. Baltimore, Williams and Wilkins, 1998. With Permission.

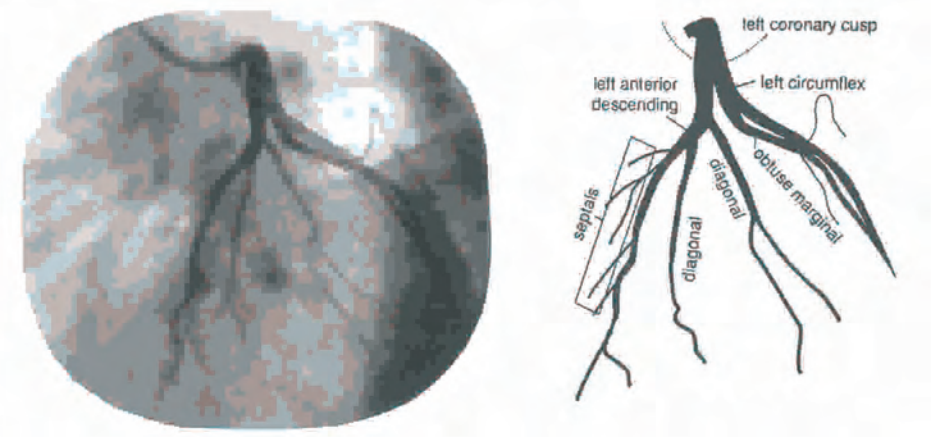

Figure 2.7: Normal radiographic anatomy of the LCA and its branches as seen in the left anterior oblique projection with a 20 degrees cranial angulation. From: Pepine CJ, Lambert CR, Hill JA: Coronary Angiography. In: Pepine CJ, Hill JA, Lambert CR (eds). Diagnostic and Therapeutic Cardiac Catheterization, 3rd ed. Baltimore, Williams and Wilkins, 1998. With Permission.

posterior descending (PDA) and posterolateral (PL) branches (Figs. 2.8, 2.9). The normally "dominant" RCA system also supplies a branch to the right atrio-ventricular node and the PDA supplies septal perforators to the inferior portion of the septum. (In 15% of the general population, the Cx is "dominant" and supplies the PDA branch that travels in the posterior

interventricular groove). The AcM branch of the serves as the boundary between the proximal and mid portion of the RCA. Thus, the portion of the artery prior to the origin of the AcM is known as the proximal RCA, while the segment just beyond the AcM is the mid RCA; the vessel halfway between the AcM and the origin of the PDA is called the distal RCA.

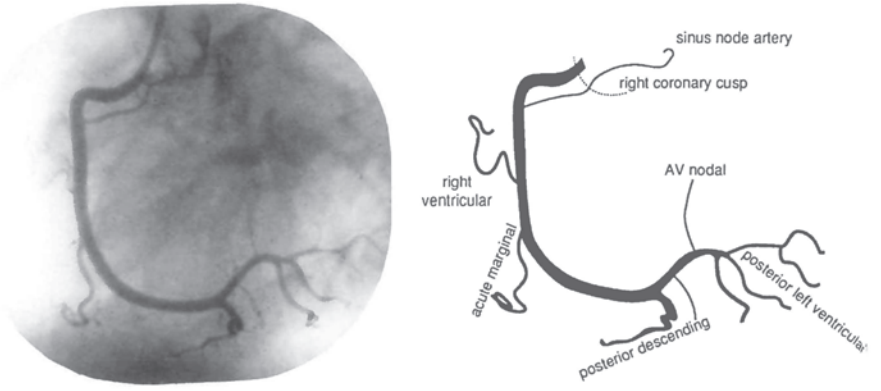

Figure 2.8: Normal radiographic anatomy of the RCA and its branches as seen in the left anterior oblique projection. From: Pepine CJ, Lambert CR, Hill JA: Coronary Angiography. In: Pepine CJ, Hill JA, Lambert CR (eds). Diagnostic and Therapeutic Cardiac Catheterization, 3rd ed. Baltimore, Williams and Wilkins, 1998. With Permission.

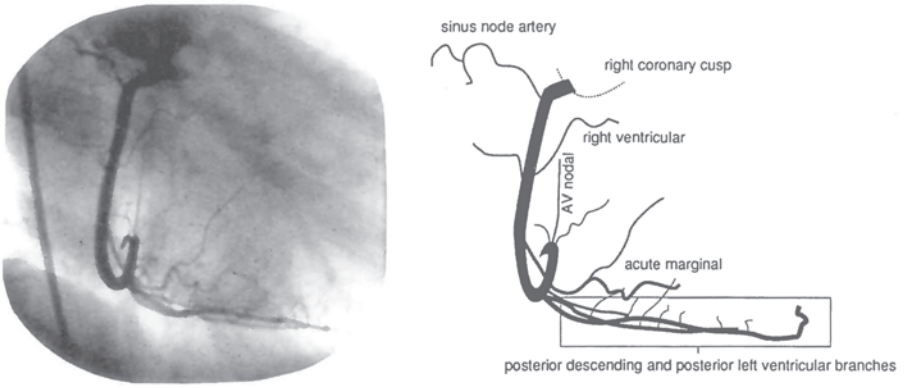

Figure 2.9: Normal radiographic anatomy of the RCA and its branches as seen in the right anterior oblique projection. From: Pepine CJ, Lambert CR, Hill JA: Coronary Angiography. In: Pepine CJ, Hill JA, Lambert CR (eds). Diagnostic and Therapeutic Cardiac Catheterization, 3rd ed. Baltimore, Williams and Wilkins, 1998. With Permission

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3) Clark JM, Glasgov S: Transmural organization of the arterial media. Arteriosclerosis 1985;5:19-34

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3

Pathophysiology Of Atherosclerotic Arterial Disease

Atherosclerosis is a degenerative disorder of the major human elastic and muscular arteries. It is characterized by the formation of intimal plaques consisting of lipid accumulations, smooth muscle and inflammatory cells, connective tissue fibers, and calcium deposits. Morbidity associated with atherosclerosis results from plaque enlargement or degeneration, with consequent impairment or cessation of blood flow. Medial atrophy, often associated with atherosclerotic disease, may also result in a weakening of the arterial wall with aneurysmal dilatation, mural thrombosis, and even vessel rupture (I).

Epidemiologic Factors (2)

Major Factors

1) *Hypertension:* Most surveyed populations show a close association between hypertension and atherosclerosis. Besides an increased risk for coronary artery disease, high blood pressure is associated with a heightened susceptibility to peripheral and cerebrovascular involvement, as well as chronic renal insufficiency. The relationship between the vascular involvement and hypertension is continuous - each increment of pressure increases the risk of vasculopathy.

2) *Hypercholesterolemia:* This is a frequent single factor associated with atherosclerosis. Several prospective population surveys now support the argument that elevated serum lipids lead to, or contribute substantially to, the development of atherosclerosis. In fact, the patient's risk of developing atherosclerosis increases exponentially at high levels of serum cholesterol. Furthermore, cardiovascular mortality increases almost linearly with progressive elevations in serum cholesterol levels, especially in the younger patients.

3) *Cigarette smoking:* There is a remarkably consistent and positive relationship between death from atherosclerosis and cigarette smoking. The risk for coronary events is more than three-fold greater in men smoking more than one pack a day than in non-smokers.

Minor Factors

These factors have a more variable correlation with atherosclerotic disease. They include diabetes mellitus, obesity, hypertriglyceridemia, hyperuricemia, sedentary lifestyle, psychosocial tensions, and a family history of the disease.

Theories of Pathogenesis

While there is a large body of descriptive clinical and experimental knowledge with regard to the general appearance of the atherosclerotic lesions, the precise initiating and perpetuating pathogenic mechanisms remain obscure. Factors that determine human lesion composition, rate of lesion enlargement, lesion organization and lesion disruption still remain to be elucidated. Several hypotheses have been proposed for the pathogenesis of atherosclerosis. Although each explanation is usually presented as a self-contained concept, there is considerable overlap in the elements of these theories (3).

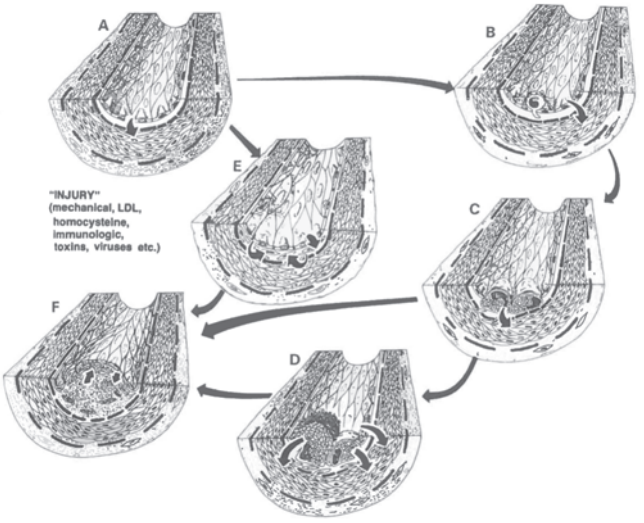


Figure 3.1 : The response-to-injury hypothesis. Advanced intimal proliferative lesions of atherosclerosis may occur by at least two pathways. The pathway demonstrated by the clockwise long arrows has been observed in experimentally induced hypercholesterolemia. Injury to the endothelium (A) may induce growth factor secretion (short arrow). Monocytes attach to endothelium (B), which may continue to secrete growth factors (short arrow). Subendothelial migration of monocytes (C) may lead to fatty streak formation and release of factors such as platelet-derived growth factor (PDGF-short arrow). Fatty streaks may become directly converted to fibrous plaques (long arrow, C to F) through release of growth factors from macrophages &/or endothelial cells. Macrophages may also stimulate or injure the overlying endothelium. In some cases, macrophages may lose their endothelial cover and platelet attachment may occur (D), providing 3 possible sources of growth factors - platelets, macrophages & endothelium (short arrows). Some of the smooth muscle cells in the proliferative lesion itself (F) may form and secrete factors such PDGF (short arrows). An alternate pathway is shown by arrows from E to F. In this case, the injured endothelium remains intact. increased endothelial turnover may result in increased growth-factor formation by the endothelial cells (A). This may stimulate migration of smooth muscle cells from the media into the intima, along with endogenous production of PDGF by these smooth muscle cells & the injured endothelium (E). These interactions could then lead to the formation of fibrous plaques and lesion progression (F). From: Ross R. The pathogenesis of atherosclerosis - an update. N Engl J Med 1986;314:488-500. Copyright 1986, Massachusetts Medical Society)

Injury Hypothesis

In the normal artery, the endothelial cells form a continuous monolayer that regulates the passage of substances from the plasma to the underlying arterial wall. Atherogenesis is seen to

begin with an endothelial injury in the form of hypertensive pressure, hemodynamic shearing forces, thrombosis, mural stimuli, chemical irritation, immunologic trauma, hypoxia, or lipid build up. Such an injury disrupts or stimulates the endothelium, and brings about a multi-phasic response that ultimately produces the atherosclerotic plaque. The endothelial cell injury permits plasma constituents like lipoproteins to have easy access to the artery wall. Injury of a sufficiently severe magnitude alters the thrombo-resistant character of the luminal lining, allowing platelets and leukocytes to directly interact with the sub-endothelial connective tissue. This triggers an important proliferative response in the media and subintimal smooth muscle cells, probably related to the release of growth factors from adherent platelets, monocytes or from the endothelium itself (Fig.3.1). With disease maturation, there is a fibrous transformation of the vascular wall brought about by increased collagen synthesis and matrix accumulation. The resulting scarring and thickening can cause arterial wall hypoxia triggering subsequent changes of inflammation and necrosis.

Lipid Hypothesis

The pivotal role of lipids or lipoproteins in the initiation and development of atherosclerosis is the key to the lipid hypothesis. Certain lipoproteins can stimulate smooth muscle replication before being metabolized into component lipids by intracellular enzymes. The belief that these lipids play a pivotal role in atherogenesis forms the basis for this hypothesis. The validity of this is strengthened by the demonstration of serum lipids and lipoproteins in the regions of developing plaques in amounts corresponding to the severity of the disease. In advanced lesions, the lipid accumulation is mainly cholesterol, especially its esterified form. Distinct changes in the arterial wall metabolism that may favor the production of certain cholesterol esters have been documented in atherosclerosis. Although the quantity of these products of altered metabolism is small, they are known to elicit the cellular responses seen in fibrous plaques. The lipid theory thus assumes that serum lipids - in particular, cholesterol and low density lipoproteins - can both initiate and mature the lesions of atherosclerosis.

Monoclonal Hypothesis

This theory views each arterial plaque as a benign "tumor" arising from a single smooth muscle cell. Proof for this concept is found in the monotypic enzyme pattern of plaque tissue from heterozygous individuals, as compared with the bimorphic values seen in undiseased arterial walls. Factors that bring about smooth muscle transformation are considered mutagens, and the progression of replication occurs under conditions that stimulate cell proliferation. The maturing process of fibrosis, calcification, necrosis and thrombosis is the same as in the other hypotheses.

Localization of Atherosclerotic Lesions

Several major arteries are particularly prone to the development of atherosclerosis. The coronary arteries, carotid bifurcation, infrarenal abdominal aorta, and the iliofemoral vessels are particularly susceptible, while the mesenteric, renal, intercostal and internal mammary arteries are relatively resistant. Such differences have been attributed to local differences in vessel wall metabolism, structure and permeability, and to differences in local hemodynamic patterns. A number of hemodynamic variables can account for the pattern of plaque distribution. These include low wall shear stress (a measure of the tangential drag force produced by the blood moving across the endothelial surface), hypertension, turbulence, flow separation & stasis, and oscillation of shear stress vectors.

Structure of Atherosclerotic Lesions

Based on morphologic appearance and composition, human lesions are usually classified as *early lesions, fibrofatty plaques and complicated plaques (4, 5)*.

1. The *early or precursor lesions* include fatty streaks, gelatinous lesions and mural microthrombi.

Fatty Streaks

These are relatively flat, fairly well demarcated patches or minute yellow foci which may appear soon after birth and are seen on the luminal surface of the aorta of most individuals over the age of 3 years. They increase in number and are most numerous around puberty. These findings are not, however, limited to young persons, and may be seen at any age, adjacent to or even superimposed on fibrous plaques. Fatty streaks have an intact endothelial cover beneath which is a "pool" of matrix in which are embedded the fat-laden cells (derived from smooth

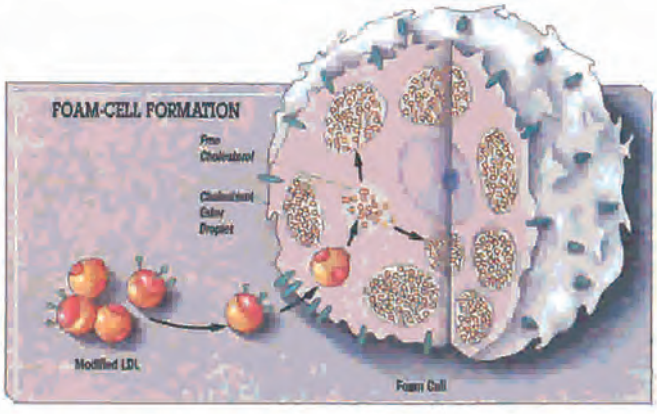


Figure 3.2 : Genesis of the foam cell. From: Grundy S (ed) Cholesterol and Atherosclerosis. Philadelphia, J. P. Lippincott Company, 1990.

muscle cells - myogenic foam cells - and blood monocytes : Fig. 3.2). There is no fibrotic component to these lesions (Fig. 3.3). Their actual significance is debated as it is not clear whether they are precursors of fibrofatty plaques or not. Many of them are probably evanescent, and the cells are not monotypic with respect to isoenzyme content. These findings suggest that focal events occurring in *some* fatty streaks result in cellular proliferation and progression while most other fatty streaks may resolve spontaneously.

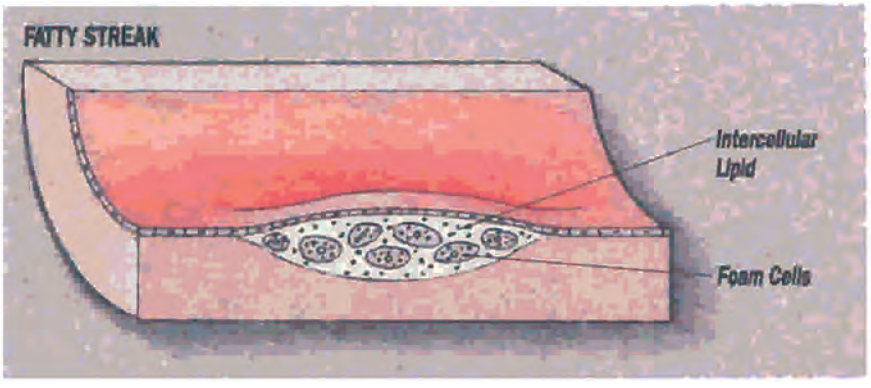


Figure 3.3 : Foam cells constituting the fatty streak. From: Grundy S (ed) Cholesterol and Atherosclerosis. Philadelphia, J. P. Lippincott Company, 1990.

Gelatinous Lesions

These are elevated lesions with an edematous swelling of the intima. The connective tissue is separated and there is a paucity of cells. These lesions have not been well characterized, but are believed to be soft, translucent thickenings, with little or no lipid, that eventually undergo a transition to fibrofatty plaques.

Mural microthrombi

Fresh mural microthrombi have been described. An occasional microthrombus has been seen to be incorporated within the vessel wall. However, the pathobiologic significance of these lesions is not clear, since it is very doubtful if contact between normal platelets and normal endothelial cells can promote functional changes in either.

2. *Fibrofatty Plaques (atheromas)* are first seen by the second decade of life, and become the predominant lesion only by the fourth decade. The fibrous plaque is grossly white; it becomes elevated and may protrude into the vessel lumen. The endothelium is intact over the lesion. Just beneath the endothelium there is a relatively compact zone of connective tissue fibers and smooth

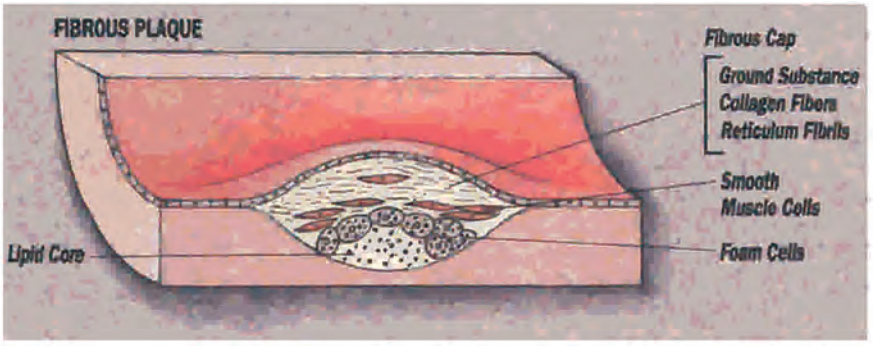


Figure 3.4 : Fibrous plaque, showing the lipid core and the overlying fibrous cap. From: Grundy S (ed) Cholesterol and Atherosclerosis. Philadelphia, J. P. Lippincott Company, 1990.

muscle cells known as the *fibrous cap*. This covers a deeper zone of variable composition and consistency known as the *necrotic core or center* (Fig. 3.4). It contains amorphous debris, lipid containing cells (resembling smooth muscle cells or macrophages), extracellular lipids, calcium

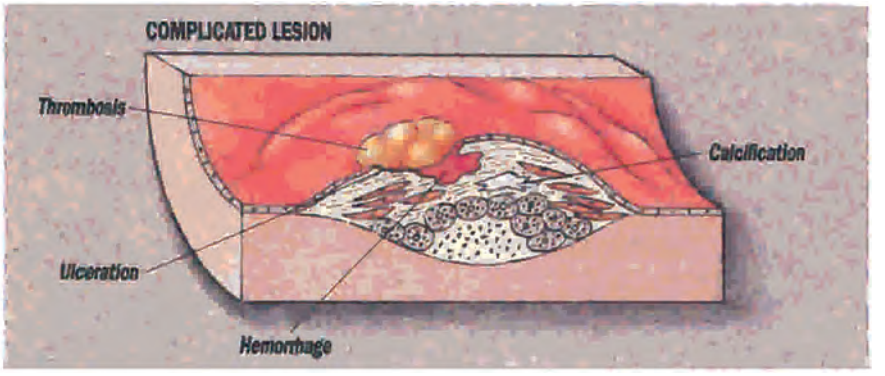


Figure 3.5 : Complicated lesion, showing calcification, ulceration, hemorrhage, and thrombosis. From: Grundy S (ed) Cholesterol and Atherosclerosis. Philadelphia, J. P. Lippincott Company, 1990.

salts and myxoid deposits. Matrix fibers and an amorphous ground substance are also present. For a necrotic core to form, a critical thickness of 100 - 200 μ is required in the intima of the coronary arteries. This critical thickness may be related to the limitation of the diffusion of nutrients from the lumen. Vasa vasorum penetrate from the adventitial or luminal aspect and supply the plaque. Sometimes, the media gets thinned out and attenuated below the intimal lesion, resulting in aneurysmal bulges. Advanced plaques show a great deal of calcification, and depending on the composition these advanced lesions are called fibrocalcific, lipid-rich, fibrocellular, necrotic, myxomatous, etc.

3. *Complicated plaques* are lesions that become exceedingly complex with time; the intimal surface may disintegrate, fissure or ulcerate favoring the formation of thrombi or the penetration of blood into the lesion. Such thrombi may get organized and further encroach on the arterial lumen. Intra-lesional hemorrhages can cause an abrupt increase in plaque volume with sudden local occlusion of the vessel, or fragmentation of the plaque and distal embolization of atheromatous fragments (Fig. 3.5).

The architecture of the plaque is important relative to interventional procedures and restenosis. Plaque formation and growth are processes resulting from both proliferative and degenerative phenomena. The proliferative processes dominate, and smooth muscle cell proliferation & collagen synthesis are the central features of plaque growth. Smooth muscle cell proliferation is under the control of several growth factors derived from activated macrophages, platelets, endothelial cells, fibrinogen-degradation products, and the smooth muscle cells themselves. Control over these processes is likely to be the central key to the progression of atherosclerosis as well as the pathogenesis of restenosis (Fig. 3.6).

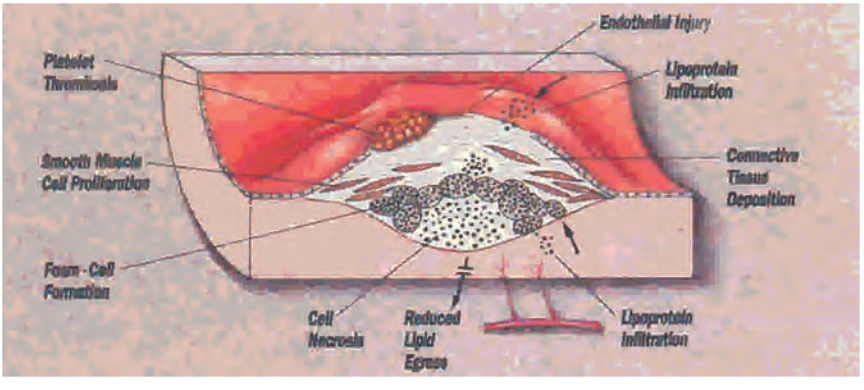
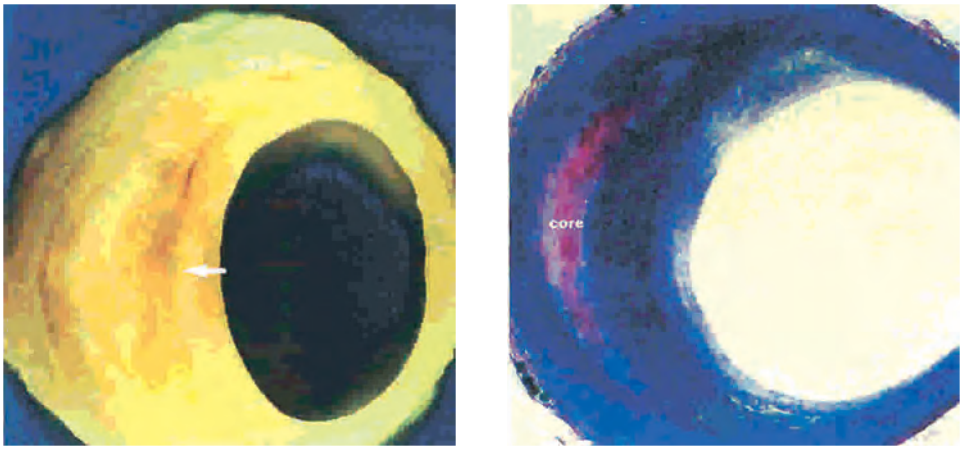


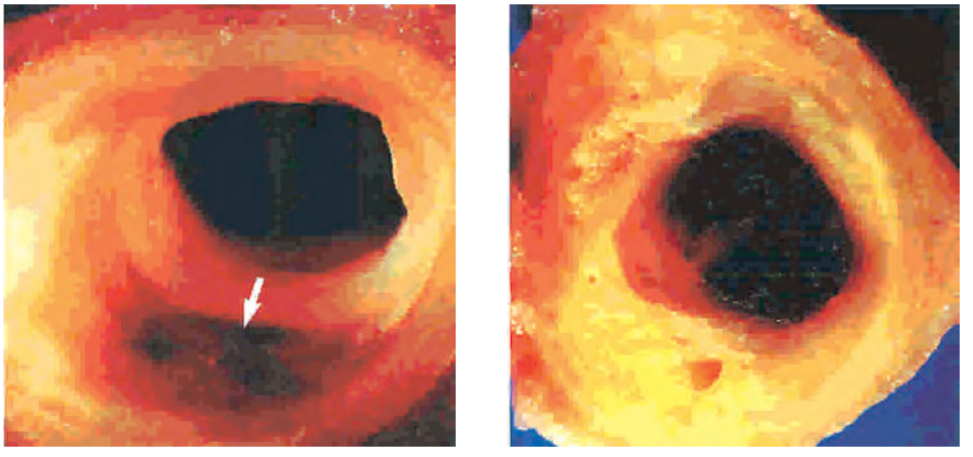
Figure 3.6: Composite representation of the pathogenesis of a complicated atherosclerotic lesion. From: Grundy S (ed) Cholesterol and Atherosclerosis. Philadelphia, J. P. Lippincott Company, 1990.

From the point of endovascular brachytherapy, it is important to appreciate that plaque distribution is quite eccentric (Figs. 3.7a - d) and can actually spiral along the vessel circumference as one proceeds along the length of the artery. Thus, at different levels of the artery, the plaque may actually occupy a different sector of the circumference of the arterial wall. This eccentric nature of the plaque does not allow for true source centering in relation to the radiation target (? external elastic lamina), even if the source is centered within the arterial lumen. This has resulted in an ongoing debate regarding the true value of source centering in the coronary arteries. However, it is quite clear that, despite all the inherent limitations, source

centering does improve dose distributions. This is especially true in the larger peripheral arteries, dialysis shunts and subclavian veins, where centering is likely to provide more effective control of restenosis (by avoiding "cold areas") while potentially lowering the risk of late vascular complications (from "hot spots").



Figures 3.7a - d : Examples of Atherosclerotic Lesions - Note the marked eccentricity of the lumen and the extremely complex lesion composition. From: Stary HC. The evolution of human atherosclerotic lesions. West Point PA, Merck & Co. 1993, with permission.



Clinicopathological Correlation:

l) Acute or unstable ischemic coronary syndromes (6)

Lesion disruption (and subsequent intraluminal thrombosis) is the key process in the development of unstable coronary syndromes. The degree of lesion disruption determines the severity of the ensuing clinical state. If only the endothelial surface is disrupted, the thrombogenic stimulus is limited, there is mural thrombus formation (without any symptoms) and gradual lesion growth. Deeper disruptions with fissuring result in a transient thrombotic occlusion (lasting a few minutes); this process may actually be repeated several times. Clinically, this manifests as unstable angina, and the pathological correlate of this is seen in the layered thrombi overlying fissured lesions in thrombosed arteries in patients with infarction or even sudden death. If the ulceration is very deep, or if the disruption exposes the lipid core, collagen,

tissue factors and other elements, a relatively persistent (few hours) thrombotic occlusion may result in an acute infarction. Angiographic studies reflect this sequence of events. The angiographic findings associated with unstable syndromes include marked eccentricity, narrow neck or an abrupt shoulder with overhanging edges and scalloped irregular, rough, or sawtooth borders, and appear to represent lesion disruption with/without a partially occlusive thrombosis. Transient vasoconstriction is common. Angiograms performed a few hours after an acute infarction typically show contrast staining or pooling suggestive of a thrombus at the site of acute occlusion. Ulceration of the infarct-related lesion is probably due to rupture of the lesion and is indicative of continued instability.

2) Chronic stable angina and silent occlusion (6)

The angiographic morphology associated with chronic stable angina is similar to that of uncomplicated lesions on postmortem studies. These lesions have a smooth outline and tapered shoulders, and appear symmetric or eccentric with a broad neck. Severely stenotic lesions tend to be fibrotic and stable. Though these lesions tend to progress to total thrombotic occlusion three times more frequently than less severe stenoses, they are much less frequently associated with infarction, probably because of well developed collaterals.

Atherosclerotic Arterial Enlargement

The formation of intimal plaque does not necessarily lead to stenosis of the arterial lumen. The affected arteries may compensate for increasing plaque deposits by enlarging, and such enlargement can maintain a normal or near-normal lumen caliber (Fig. 3.8). This was first reported by Mann in 1972 in his studies of the African Masai tribesmen. Glasgov concisely refined the principles of atherosclerotic artery growth and used the term "compensatory enlargement" (7). Similar phenomena have also been observed in animal models. This enlargement may be an adaptive response as a result of the increased wall shear stress or can be secondary to medial atrophy with consequent bulging of the vessel wall. However, this arterial expansion ceases after a threshold plaque size is reached. When the cross-sectional area of the plaque exceeds approximately 40% of the area encompassed by the internal elastic lamina, further plaque growth narrows the lumen proportionally. This size change is now termed "remodeling" and is considered in greater detail later on.

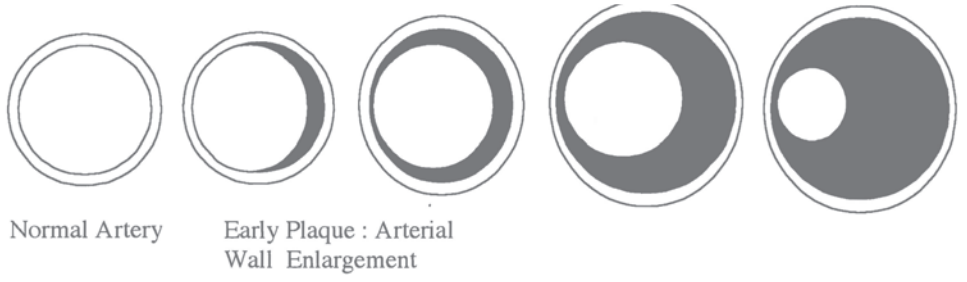


Figure 3.8 : Possible sequence of changes in atherosclerotic arteries in response to enlarging atherosclerotic plaques. In the early stages of intimal plaque deposition, the lumen remains normal or enlarges slightly (left). When the plaque enlarges to involve the entire circumference of the vessel and produces more than 40% stenosis, the artery is no longer able to enlarge at a rate sufficient to prevent luminal narrowing. Adapted from: Glasgov S, Weisenberg BA, Zarins CK et al. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371-137. Copyright Massachusetts Medical Society, 1987.

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4

Angioplasty, Stents And Adjuncts

The essential elements of an angioplasty procedure include:

1) Access to the arterial circulation.
2) Detailed assessment of the pathologic anatomy, via a diagnostic angiogram.
3) Performance of the actual angioplasty.
4) Post-angioplasty evaluation.

Access to the Arterial Circulation

The coronary and femoropopliteal arteries are usually accessed via the femoral route, employing the Seldinger technique (Fig. 4.1). The site is chosen 1 - 2 cm. below the inguinal ligament. Following infiltration with a local anesthetic, small skin nicks are made over the proposed puncture site(s); these may be enlarged and deepened with the tips of a curved hemostat. The femoral artery is located by feeling the pulse (special techniques, including the use of a Smart Needle which has an obturator incorporating an ultrasound crystal, are required if there is no pulse). The I8-gauge thin walled Seldinger needle consisting of a blunt, tapered external cannula with a sharp solid projecting obturator, is inserted into the artery, the obturator withdrawn and an appropriate guidewire is advanced carefully through the needle.

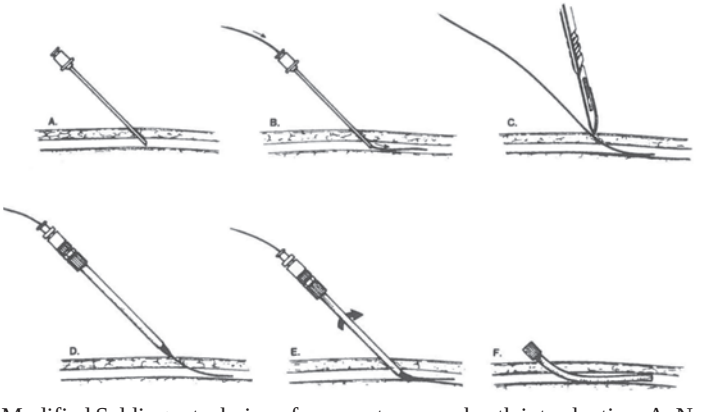

Figure 4.1 : Modified Seldinger technique for percutaneous sheath introduction. A. Needle puncture of vessel. B. Flexible guidewire advanced into vessel. C. Needle removed, guidewire left in place, and hole in the skin enlarged with scalpel. D. Sheath and dilator threaded over guidewire. E. Sheath and dilator advanced over guidewire into vessel. F. Guidewire and dilator removed, while sheath remains in place. From: Hill JA, Lambert CR, Vlietstra RE Pepine CJ. Review of General Catheterization Techniques. In: Pepine CJ, Hill JA, Lambert CR (eds). Diagnostic and Therapeutic Cardiac Catheterization, 3rd ed. Baltimore, Williams and Wilkins, 1998. With permission.

The Diagnostic Angiogram

The protruding wire is carefully wiped and threaded into the lumen of a sheath and dilator combination adequate to accept the catheters to be used later. Almost all sheaths have a side arm and incorporate a design to prevent bleeding around the catheter. An appropriate angiographic or guiding catheter is introduced through the sheath and a detailed diagnostic study is performed. Multiple different views are often necessary to delineate the pathology in full detail.

Angiographic Assessment Before Angioplasty

1. Lesion severity
   - Degree of stenosis
   - Length of stenosis
2. Lesion morphology
   - Eccentricity, thrombus, calcium
   - Complex lesions
3. Branches
   - Lesion-associated branches with/without stenosis
   - Vessel-associated branches potentially affecting guidewire passage
4. Collateral supply
   - Presence and extent of collaterals
   - Presence and extent of disease in collaterals supplying target artery
5. Proximal artery characteristics
   - Origin, course and size of artery containing the lesion influences the catheter selection
6. Distal "run-off'.

Characterization of Lesion Suitability In The Coronary Arteries (AHA/ACC Classification) (4)

- Type A (Minimally complex):

  Discrete length, < 10 mm
  Concentric
  Readily accessible
  Nonangulated segment (< 45 degrees)
  Smooth contour
  Little/No calcification
  Less than totally occlusive
  Not ostial in location
  No major side branch involvement
  No thrombus

- Type B (Moderately Complex):

  Tubular (l0 - 20 mm)
  Eccentric
  Moderate tortuosity or proximal segment
  Moderately angulated segment (45 - 90 degrees)
  Irregular contour
  Total occlusions < 3 months old

Ostial
Bifurcation lesions requiring double guidewires
Some thrombus present

- Type C (Severely Complex):

  Diffuse length (> 20 mm)
  Excessive tortuosity of proximal segment
  Angulation > 90 degrees
  Total occlusion > 3 months old and/or bridging collaterals
  Inability to protect major side-branches
  Degenerated vein grafts with friable lesions

Outline of the Angioplasty

Following the diagnostic study, the angiographic catheter is withdrawn, and a special guidewire is negotiated across the site of obstruction. An angioplasty balloon catheter is then threaded over this guidewire, and the balloon positioned to lie across the narrowed segment. The balloon inflated till an adequate lumen is established (Fig. 4.2).

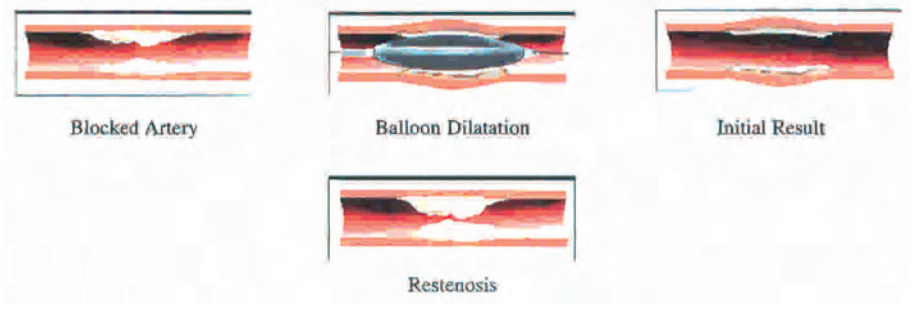

Figure 4.2 : Outline of angioplasty, and the problem of restenosis

Post-procedure Evaluation

This can be done in several ways. Measuring pressure gradients in one such approach. Intravascular ultrasound (IVUS) is another very useful tool for evaluating residual plaque, post-procedure minimal lumen diameter (MLD), adequacy of stent deployment, complications such as dissections, etc. However, the most common method of assessing the adequacy of the angioplasty is by post-procedure angiography with evaluation of the MLD. The following features are usually assessed:

- Resultant lesion

  Usually assessed by MLD and Percent Residual Stenosis with/without contrast flow compromise. The presence/absence of flow compromise is described by the *Thrombolysis In Myocardial Infarction* (TIMI) grade:

  - ➢ TIMI 0 (No perfusion) - No antegrade flow beyond point of occlusion
  - ➢ TIMI 1 (Penetration without perfusion) - Contrast material passes beyond point of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of cineangiographic filming sequence.

- ➢ TIMI 2 (Partial perfusion) - Contrast passes across obstruction and opacities coronary bed distal to obstruction, or its rate of clearance from distal bed (or both) is perceptibly slower than its entry or clearance from comparable areas not perfused by previously occluded vessel, e.g. opposite coronary artery or coronary bed proximal to obstruction.
- ➢ TIMI 3 (Complete perfusion) - Antegrade flow into bed distal to obstruction occurs as promptly as antegrade flow into bed proximal to obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or opposite artery.

- Lesion morphology
  - ➢ Split or dissection : Type A = Small radiolucent area within the vessel lumen
    Type B = Linear, non-persisting extravasation of contrast
    Type C = Extramural, persisting extravasation of contrast
    Type D = Spiral filling defect
    Type E = Persistent lumen defect; delayed antegrade flow
    Type F = Filling defect with total coronary occlusion
  - ➢ Thrombus (Present/absent)
- Distal / adjacent vessels
  - ➢ Associated branch damage
  - ➢ Emboli

Coronary Angioplasty

Coronary angioplasty presents its own unique set of problems and constraints. A brief overview of the involved instrumentation and an outline of the actual procedure are presented here (1, 2). A basic coronary angioplasty system consists of three components: a) a *guiding catheter,* which provides a stable access to the coronary ostium, a route for contrast injection, and a conduit for the advancement of the dilatation equipment; b) a *leading guide wire* that can be negotiated through the guiding catheter, across the target lesion, and well into the distal coronary vasculature to provide a rail over which a series of therapeutic devices can be advanced; c) a nonelastomeric *balloon dilatation catheter* filled with liquid contrast medium.

Dilators

A vascular dilator is used to create a track from the skin through the vessel wall to allow for the subsequent atraumatic passage of sheaths and catheters. The dilator is made of hard plastic, usually Teflon or polyethylene, to allow passage through fibrous tissue or atherosclerotic or calcified arterial walls. The tip tapers smoothly to minimize the possibility of tearing the arterial wall. However, the final tip taper and internal diameter of the dilator should closely fit the guidewire diameter to allow smooth advancement of the dilator over the wire, with little blood between the wire and dilator lumen and minimal trauma to the vascular wall. Dilators are available in various lengths and diameters (French sizes).

Guidewires

The basic guidewire consists of a solid core (or mandrel, made of stainless steel or nitinol) that is ground to a progressive taper in its distal portion. Guidewires usually have an external

coating of Teflon. This provides "lubricity" (i.e., a reduction in friction between wire and catheter lumen) and reduced thrombogenicity. Other more recent designs incorporate an elastic alloy core coated with a polyurethane jacket and a hydrophilic coating. This provides for a pliable tip, a smooth outer coating, and excellent torque control. Guidewires are available in lengths ranging from 5 cm to 260 cm. In general, a guidewire should be at least 20 cm longer than the catheter for which it to be used. Double length (300 cm) exchange wires are also available; these allow for easy exchange of one device for another. External diameters of the guidewires range from 0.010 inch to 0.038 inch. The larger the wire, the more steerable it is, and the greater the allowable push for crossing a total occlusions. The smaller, 0.012 - and 0.010 - inch wires are less steerable, but are compatible with a lower profile series of balloons, and are potentially useful in crossing more distal or severe lesions, or can be used with smaller French-size guiding catheters. Guidewires also vary widely in the stiffness of their tip. The more rigid steerable wires are particularly useful for steering (torqueability) and for crossing total occlusions and/or recanalized channels that often require greater force to cross the lesion. Conversely, the more flexible and floppy wires, while less steerable, are also less traumatic for crossing complex unstable lesions, graft stenoses, or for recrossing lesions immediately after dilatation. Guidewire tips can have a J-configuration. These J wires are described by the radius of curvature in the tip (e.g., 3 mm “J”). The 3 mm J is indicated for routine use, and has advantages over straight wires in its tendency to avoid entering side branches and to curve or "glance off" of atherosclerotic plaques, rather than dissect beneath them. With obstructive plaques in highly tortuous vessels, a larger J is sometimes helpful in order to avoid traumatic guide-wire advancement.

Vascular Sheaths

Previously, most arterial catheterizations were done via an open cutdown technique, or by the Seldinger technique, with catheter insertion directly over a guidewire. Current interventional techniques (while incorporating the basic Seldinger technique for vascular access) employ a thin walled vascular sheath, which is advanced over the wire into the femoral artery. There are several advantages inherent in the use of these sheaths: catheter changes are rapid, and there is reduction of arterial trauma and the possibility of bleeding into the subcutaneous tissues during the catheterization procedure. Following use of thrombolytic and anticoagulant agents, the sheath may be left in place until coagulation status has returned to baseline or has been reversed by protamine. The sheath may also be left in place to allow for rapid vascular access, as in unstable cases, or following PTCA, when reocclusion is a possibility and an emergency repeat dilatation may be necessary.

Vascular sheaths come in a variety of lengths and sizes. Size ranges from 5 Fr through 14 Fr are available, while the lengths range from 6 cm to 25 cm. In sheaths with side extensions, the tubing is polyethylene and extends to a 3-way stopcock, providing separate ports for pressure monitoring and flushing or administering medications. The sheath itself is made of a non thrombogenic material, usually Teflon or polyethylene, which is extremely strong, thin, pliable, and radiolucent. The tip of the sheath is tapered to minimize trauma as the sheath is advanced into the vessel. Sheaths also incorporate a variety of hemostatic valves.

Catheters

Given the demands placed upon them, it is not surprising that catheters are extremely diverse in shape, design, and specific features. This section will review some of the terminology used to describe catheters. Listed below is a short glossary of terms that are frequently encountered in product literature:

- Axial control - Ability to transmit forces from the end of the catheter to the tip.
- Body - Segment of catheter between the tip and hub.
- Flexibility - Ability of a section of catheter to bend on contact with a resistant surface.
- Hub - Fitting on the proximal end of the catheter.
- Internal diameter - Diameter of the internal lumen of the catheter.
- Maneuverability - Ability to advance a catheter around sharp bends or through tortuous vascular segments
- Memory - Ability to recover and maintain a specific configuration after insertion and guidewire removal.
- Pliability - Ability to bend and to be shaped.
- "Pushability" or power - Ability to directly transmit force applied to the hub of the catheter longitudinally to the tip. (Of considerable importance in balloon angioplasty catheters.)
- Radio-opacity - Ability to visualize the catheter under x-ray fluoroscopic control.
- Softness - Ability to easily bend.
- Stability - Ability of a catheter to remain in position.
- Stiffness - Ability to resist bending, a lack of flexibility.
- Strength - Ability to withstand high pressure injections.
- Support or backup - Ability to remain in position despite resistance, used in reference to angioplasty guide catheters.
- Tip - The final taper or distal end of the catheter.
- Torque control- Ability to directly transmit rotational forces from the end of the catheter to the tip.
- Trackability - Ability of a catheter to follow a guidewire along its course.

Guiding catheters

Guiding catheters remain a crucial component in PTCA. They provide a stable access to the coronary ostium, allow for contrast injection and act as a conduit for the various interventional devices. Their design is quite complex, since there is a need for the largest possible outer/luminal diameter ratio, while incorporating a Teflon liner to reduce friction, metal or plastic braid to transmit torque, sufficient stiffness to provide "backup" support during device advancement, and a smooth outer coating to resist thrombus formation. Most guiding catheters also include a very soft material in the most distal 2 mm. of the catheter to reduce the chance of vessel trauma. 8F and 9F catheters are commonly used today. These have an internal diameter of 0.800 and 0.092 in. respectively. The standard guiding catheter is 100 cm long.

Dilatation Catheters

Several features of the dilatation catheter are important. Obviously, the diameter of the smallest opening through which the deflated balloon can be passed *(profile)* is of crucial importance in its ability to negotiate stenotic areas. Also important are the ability of the balloon to bend as it negotiates tortuous plaque segments *(trackability)*, and the presence of sufficient shaft stiffness *(pushability)* to force it through stenosis. Other specialized properties include whether

the catheter travels over the wire along its full length, or just in its tip *(rapid-exchange, monorail). The monorail design is especially advantageous in endovascular brachytherapy as one can have a catheter with a closed distal end, thus preventing the source from coming into contact with blood. Catheters have also been designed with a series of side-holes in the shaft proximal and distal to the balloon segment (perfusion balloons), so as to allow antegrade flow of blood - this may again be an important consideration in endovascular brachytherapy, when the catheter could be in place for prolonged periods.* The balloons are made of a variety of different materials and have inflated diameters ranging from 1.5 to 6.0 mm. They are usually 20 mm in length, but shorter or longer balloons are available.

Procedure (3)

More than 90% of the procedures are done from the femoral approach, though the brachial route may be preferred in some patients. Patients are generally pretreated with a calcium-channel blocker and aspirin. After placement of the arterial sheath via a Seldinger technique, the patient is heparinized till an activated clotting time of 300 - 350 sec. is obtained. Baseline angiograms of

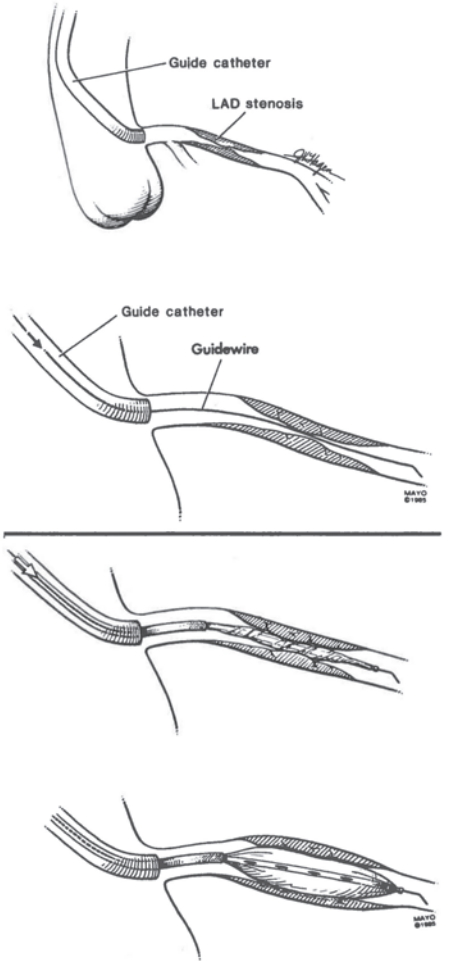

Figure 4.3 : Technique of PTCA, LAD, Left Anterior Descending Coronary Artery. From : Vliestra RE, Holmes DR, (eds) PTCA: Percutaneous Transluminal Coronary Angioplasty. Philadelphia: FA Davis, 1987. Reproduced with the permission of the Mayo Foundation

one or both coronary arteries are then obtained using diagnostic catheters or the angioplasty guiding catheter. The guiding catheter is then connected to a pressure manifold by an extension tubing and a rotating hemostatic valve (Touhy-Borst Valve). The manifold permits the maintenance of a "closed system" during pressure monitoring, catheter flushing and contrast injection. The hemostatic valve has an adjustable O-ring that allows introduction and free movement of the angioplasty balloon while maintaining a sufficient seal around the balloon catheter shaft. Once the guiding catheter is positioned in the coronary ostium, the guidewire is steered across the target lesion, guided by puffs of contrast injected through the guiding catheter. The position of the wire tip in the distal vasculature is confirmed by angiography and an appropriate sized balloon is selected (by using the adjacent nondiseased segment of the coronary artery as a reference). The prepared and flushed balloon is then guided over the guidewire and positioned within the target stenosis. The balloon is then inflated progressively using a screw-powered hand-held inflation device equipped with a pressure dial. At low pressures, the balloon typically has an hourglass appearance due to its central restriction by the stenosis. As the pressure is increased, this waist expands (gradually or abruptly) at pressures between 4 to 10 atmospheres. The result is then assessed with a repeat angiography (Fig. 4.3). The ideal end result would, of course, be complete normalization of the vessel lumen. Given the plaque composition, the usual result of a successful angioplasty is an approximately 30% residual stenosis, with some degree of intimal disruption. A more accurate assessment of the post-angioplasty area can be obtained with Intravascular Ultrasound (IVUS); this may also help select patients for further procedures like directional atherectomy or stenting. Post-procedure, once the activated clotting time has fallen below 160 sec., the sheath is removed and the site controlled my manual pressure or compression with mechanical aids. The patient typically remains in bed for 18 to 24 hours, and then ambulates before discharge.

Endovascular Stents

Stents act as a rigid internal scaffolding. Because of this, they significantly decrease the element of post-angioplasty recoil and practically eliminate any late lumen loss attributable to arterial remodeling (Fig. 4.4). In many centers, today, more than 80% of the percutaneous coronary interventions are associated with stent placement. Refined implantation techniques, improvements in stent design and simple, effective anticoagulation therapy have been critical in the widespread acceptance of coronary stenting. The reasons for increasing use of coronary stents include (5):

1) Stents provide favorable and predictable acute angiographic results.
2) They improve the safety of angioplasty by successfully treating acute and threatened closures.
3) Stents improve long-term clinical outcomes by reducing restenosis.
4) Stents are easy to use.
5) Use of stents often decreases overall procedural time.
6) Stents often provide a favorable acute angiographic result and clinical outcome in complex lesion morphologies.

Figure 4.4 : Stent Deployment

The currently available stents can be classified in several different ways: *design type* (coil, ring, slotted tube, mesh, multi-design and custom), *composition* (stainless steel, nitinol, tantalum, other), or their *mode of deployment* (balloon expandable, self expanding). Today, there are more than 55 stent types manufactured by 28 different companies (Fig 4.5). The ideal stent would include most (if not all) of the following features - flexibility, track ability, low profile, radiopaque, thromboresistant, biocompatible, reliable expand ability, high radial strength, circumferential coverage, low surface area and hydrodynamic compatibility. Needless to say, no single design incorporates all these favorable characteristics, and each one has its own strengths and weaknesses (6).

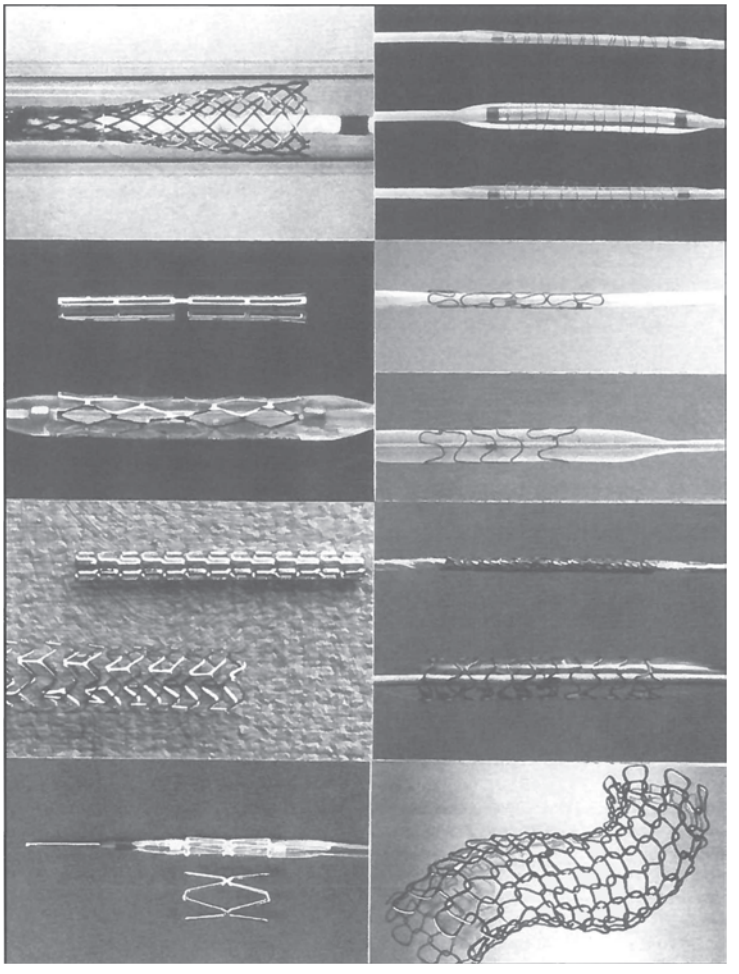

Figure 4.5: Examples of different stents. From: Baim DS, Grossman W (eds) Cardiac Catheterization, Angiography and Intervention, 5th Ed. Baltimore, Williams and Wilkins, 1996. With permission.

Several materials have been used to coat the stents. This has been done for two main reasons:

1) To reduce their inherent thrombogenicity by
   a) Placing a biologically inert barrier between the stent surface and the circulating blood, e.g. coating the stent with gold or silicon carbide.
   b) Providing a biologically active surface that interacts with the blood, by coating the stents with heparin or with monoclonal antibodies directed against platelet integrins.
   c) Passivating the stent surface, by coating it with fibrin (to provide a platform for reendothelialization), gel paving, endothelial seeding, etc.
2) To try and reduce the neointimal hyperplasia by
   a) Coating stents with antiproliferative agents, e.g. paclitaxel, rapamycin, etc.
   b) Coating stents with a polymeric matrix capable of delivering antisense oligonucleotides locally to the vessel wall to inhibit the proliferation of the smooth muscle cells.
   c) Use of radioactive stents.

Two landmark studies firmly established the role of stents in the prevention of restenosis. The Stent Restenosis Study (STRESS) randomized 410 patients to elective stenting vs PTCA alone (with stents available for"rescue"). The patients had to fit several very restrictive criteria: LVEF >40%; *single, new, discrete lesions ≤ 15 mm in length in vessels ≥ 3.0 mm in diameter;* no thrombus or diffuse disease; no vessel tortuosity or ostial stenosis or left main disease. Post-procedure, the stented vessels had a significantly larger MLD by approximately 0.5 mm when compared to the control group. This difference was maintained at the 6 month angiogram (MLD 1.74 mm vs. 1.56 mm, p =0.007). The six-month binary restenosis rate was reduced in the stent group, 31.6% vs. 42.1%, p = 0.046. Clinical follow-up showed that the event-free survival was 80.5% in the stented patients vs. 76.2% in the controls (p = 0.16) and the target lesion revascularization rate (TLR) was reduced from 15.4% to 10.6% (7). Following initial publication of the 410 patients, a further 186 patients were enrolled. At a 1 year follow-up (STRESS I and II), there was a reduction in the composite clinical endpoint of Major Adverse Cardiac Events, or MACE (death, MI, CABG and repeat angioplasty) from 18.2% in the control arm to 9.8% in the stented patients (p = 0.003). However, due to the use of a very aggressive anticoagulation regimen in the stented patients (aspirin, dipyridamole, low-molecular weight dextran and warfarin for 1 month), they had a much higher incidence of bleeding and vascular complications (8.5% vs. 4.8%, p = 0.07) (8).

In the Belgium Netherlands Stent (BENESTENT) trial, 520 patients were similarly randomized to either elective stenting or PTCA alone (with availability of "rescue" stenting). The composite clinical endpoint included death, MI, cerebrovascular accidents, CABG and repeat angioplasty of the same lesion within 6 months. At six months, only 20% of the stented patients had reached the composite clinical endpoint vs. 30% of the control patients (p = 0.02). The binary restenosis rate was 22% in the stented patients vs. 33% in the controls (p = 0.02). However, bleeding and vascular complications continued to predominate in the stented patients (13.5% vs. 3.1 %, p < 0.001) (9).

Early in the days of stent implantation, operators were very concerned about the risk of stent thrombosis, and the attendant risks of MI and death. Aggressive anticoagulation regimens were employed, including aspirin, dipyridamole, warfarin, heparin and low-molecular weight dextran. Not only did this result in a high incidence of bleeding and vascular complications, but stent thrombosis rates still remained high at 2.6-15%. Columbo and colleagues reported a substantial reduction in stent thrombosis to 1.6% by employing high pressure inflation technique (average 15 atmospheres), followed by intravascular ultrasound (IVUS) to ensure that the stent was optimally and uniformly apposed to the vessel wall (the basic concept was that if stents were poorly apposed to the vessel wall, there would be "gaps" between the stent and the vessel wall where blood could get "trapped" and form a nidus for thrombus formation). In their study, patients received a very simple anticoagulation regime consisting of aspirin and ticlopidine (10). These, and other, observational studies were followed by two important randomized trials - ISAR and STARS. Both confirmed a stent thrombosis rate of only 0.6-0.8% with optimal stent deployment and the combination of aspirin and ticlopidine (11, 12).

Currently, the use of stents for FDA-approved and non-approved indications has continued to grow. Available data strongly support the use of stents in STRESSI/BENESTENT types of lesions, and also certain non-approved lesions, such as some patients with small vessels and acute MI. patients with diffuse disease, bifurcation lesions, heavily calicific lesions, and ostial stenoses continue to pose a major clinical problem. Customized stents continue to evolve for specific situations.

Figure 4.6 : In-stent Restenosis

Unfortunately, while the stents have been very effective in creating a larger final lumen, and in opposing any recoil or negative remodeling, these benefits accrue at the expense of an increase in neointimal proliferation. It is believed that the stent struts (that "protrude" into the vessel wall), may be acting as a chronic "irritant" resulting in an increase in neointima production. This has resulted in a new "disease entity": in-stent restenosis (Fig. 4.6). The natural history of in-stent restenosis is quite poor - subsequent interventions in patients with diffuse in-stent restenosis are associated with failure rates as high as 80-85% (patients with a short, focal in-stent restenosis do better: failure rates of 20 - 30%). Accordingly, a lot of current research is being focused on designing stents to function as a "drug-delivery platform" (rapamycin, paclitaxel, etc.) in an effort to inhibit this neointimal hyperplasia.

Other Mechanical Approaches

These include the use of a variety of *lasers, rotational and directional atherectomy devices, cutting balloons, etc.* to debulk the plaques. Depending on the clinical situation these can be used alone or in conjunction with balloon dilatation. While these debulking devices are capable of providing a larger lumen, in the immediate post-procedure period, several randomized trials have failed to confirm consistently superior long-term clinical outcomes with the use of any of these devices.

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5

"How Does Angioplasty Work?"

Though several hundreds of thousands of balloon angioplasties have been performed to date, it is still a little surprising that the procedure actually works. The angioplasty can ameliorate clinical symptoms by increasing the luminal cross-sectional area, leading to a decrease in resistance to blood flow. To effect this, the balloon must induce an irreversible change in the plaque or in the vessel. In biomechanical terms, maintaining a new shape after removal of a deforming force is a plastic property of the material. The elastic properties of the artery and plaque oppose effective dilatation and also complicate laboratory experiments designed to define these mechanisms.

Several mechanisms have been advanced to explain the enlargement of the arterial lumen as a result of the angioplasty (1). These include:

1) Compaction of the plaque

2) Redistributive remodeling of the plaque

3) Embolization of the plaque constituents

4) Plastic stretching of the arterial wall

5) Phagocytic removal of volume during healing (Remodeling of the "controlled injury")

Compaction of the Plaque

This was the first explanation offered for angioplasty, i.e. the plaque was actually compressed by the balloon (2, 3, 4). However, the liquids and solids composing the plaque are virtually incompressible. Thus, although a compressive force is applied to the plaque, it is unlikely that the "plaque compresses and nothing is displaced or removed".

Redistributive Remodeling of the Plaque

This implies that the volume of the plaque is rearranged to occupy much less space in the radial direction and more space in the linear direction (5). This would result in a dramatic lowering of vascular resistance (Poiseuille's law relates resistance to flow directly to the length of the tube, but inversely to the *fourth power* of the radius). This mechanism is known as the "cold flow" concept; that is, atheromatous material can

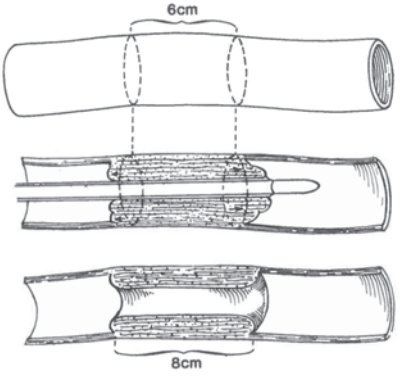

Figure 5.1 : Schematic representation of the concept of redistributive remodeling. From: Vliestra RE, Holmes DR, (eds) PTCA: Percutaneous Transluminal Coronary Angioplasty. Philadelphia: FA Davis, 1987. Reproduced with the permission of the Mayo Foundation

be molded into a configuration that permits it to serve as an autogenous, in situ graft. If the material is pushed radially as well as longitudinally, the decrease in resistance to flow is even greater (Fig. 5.1). The term "reskeletalization" was coined to describe the extensive plaque redistribution, because it emphasizes the structural role of the remodeled plaque in maintaining the shape of the artery after dilatation. Elegant as this concept is there is little experimental evidence to support it. A large number of the plaques are rock-hard and it is difficult to visualize them undergoing remodeling at pressures short of that required to rupture the vessel wall. However, not all plaques are rock-like. Also, cadaver experiments at room temperature may be misleading, since lipids in the plaque may be more fluid at body temperatures and thus more capable of being molded.

Embolization of the Plaque Constituents

The volume of the plaque would be reduced if either the liquid or particulate portions of the plaque were released by the abrasion or compression of angioplasty. The endothelium is nearly always denuded in angioplasty, but this would do little to enlarge the lumen. Similarly, the plaque frequently fragments in situ, but the lumen would only be enlarged if the plaque were actually stenting the vessel wall. Actual embolization of the fragmented plaque is fortunately a rare event, though it does happen (6). The very high pressures encountered in angioplasty could conceivably express liquid material from the plaque with consequent enlargement of the arterial lumen, without evidence of embolization. Again, there is little evidence to show that this actually happens in the context of clinical angioplasty.

Irreversible Stretching of the Arterial Wall

If plaque volume and shape are essentially unaltered, the increase in lumen is likely to occur by expansion of the arterial tube itself (Fig. 5.2). Since the plaque is primarily in the intima, the

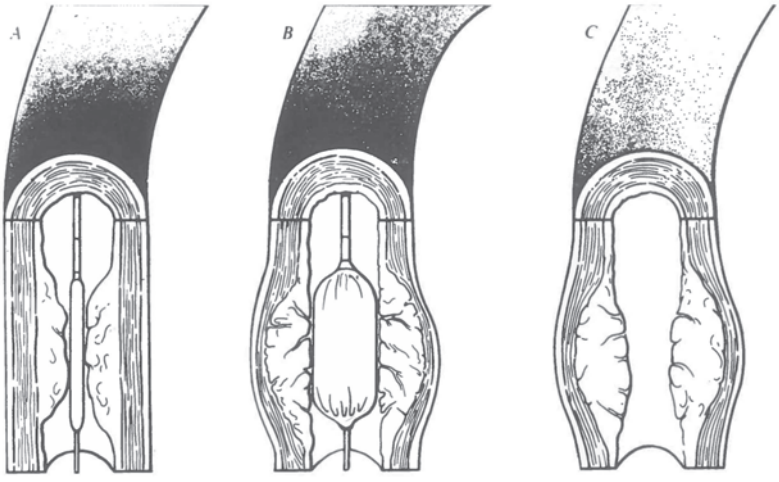

Figure 5.2 : Proposed mechanism of angioplasty. (A) Deflated balloon positioned across the stenosis. (B) Inflation of the balloon catheter within the stenotic segment causes cracking of the intimal plaque, stretching of the media and adventitia, & expansion of the vessel. (C) Post-dilatation, there is partial elastic recoil of the vessel wall, leaving a residual stenosis, and local plaque disruption which would be evident as "haziness" of the lumen contours on angiography .. From: Baim DS Coronary Angioplasty. In: Baim DS, Grossman W (eds) Cardiac Catheterization, Angiography and Intervention, 5th Ed. Baltimore, Williams and Wilkins, 1996. With permission.

media and adventitia would be expected to have near normal mechanical properties. The principle components of the arterial wall are elastin, collagen, and smooth muscle. Elastin may be stretched several hundred percent without losing its elasticity; it cannot account for the plastic change that we are seeking for. The strongest and least distensible structure in the arterial wall is collagen. It is virtually inextensible. Thus, overzealous stretching of the arterial wall can lead to aneurysm formation or even rupture. However, angioplasty might also stretch or rupture the collagen fibers that connect one smooth muscle cell to another, leaving an intact sleeve and some stretched medial bundles (7). Finally, the stretch of angioplasty could damage the contractile function of the smooth muscle cells directly. This is supported by the observation that stretching the artery in vivo by 30 - 50% abolishes the constrictor response to drugs.

Remodeling of the "Controlled Injury"

Numerous studies have shown plaque fracture immediately following angioplasty. This is shown as some fuzziness in the immediate post-angioplasty films. However, images obtained a few months after the procedure often show a much improved picture implying extensive remodeling with removal of debris (Fig. 5.3). Though this is commonly seen and may contribute to the final result, there is no instance of an actual increase in lumen diameter reported with time.

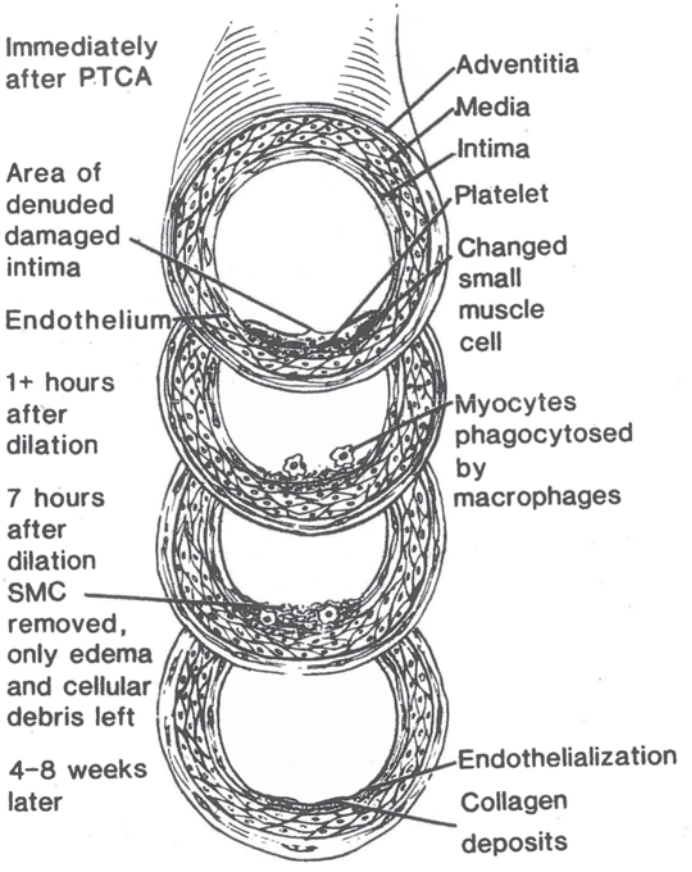

Figure 5.3 : Time course of controlled remodeling of the angioplasty "injury" with a good outcome. From: Vliestra RE, Holmes DR (eds) PTCA: Percutaneous Transluminal Coronary Angioplasty. Philadelphia, FA Davis, 1987. Reproduced with the permission of the Mayo Foundation

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6

Epidemiology & Mechanisms Of Post-PTA Restenosis

The restenosis problem is quite real; however, in any clinical setting, the exact incidence of restenosis will vary, depending on the definition of restenosis that is used (Table 1). Angiographic, hemodynamic, clinical or functional endpoints can result in widely varying rates of restenosis. The length of follow-up will also affect these figures, as will the mode of statistical analyses, as these patients are at an ongoing risk for intercurrent mortality.

Table 1

Commonly Employed Definition Of Restenosis

1. An increase of > 30% from the immediate postangioplasty stenosis to the follow-up stenosis (NHLBI-l)
2. An initial stenosis <50% after angioplasty, increasing to >70% at follow-up angiography (NHLBI-2)
3. An increase in stenosis at follow-up angiography to within 10% of the predilatation stenosis (NHLBI-3)
4. A loss of >50% of the gain achieved by angioplasty (NHLBI-4)
5. A postangioplasty stenosis of < 50% increasing to > 50% at follow-up
6. A decrease in the lesion minimal luminal diameter of > 0.72 mm from immediate postangioplasty stenosis to follow-up stenosis.

NHLBI = National Heart, Lung, & Blood Institute definition.

Following a percutaneous intervention, a higher incidence of restenosis is seen in association with several factors :

1) Anatomic site of dilatation - Proximal LAD lesions
   - Aorto-ostial native or vein graft lesions
   - Body of vein graft lesions
2) Severity of initial occlusion - Lesion length
   - Discrete : < 10 mm long
   - Tubular: 10 - 20 mm long
   - Diffuse: Lesion length ≥ 20 mm
   - Small vessels
3) Inadequacy of distal runoff.

4) Failure of the initial PTA in restoring an adequate lumen and laminar flow.
   - Incomplete dilatation
   - Elastic recoil
5) Extensive injury to the vessel wall.
6) Exuberant proliferative/remodeling response to the injury (Determined by other medical conditions like diabetes mellitus, etc).
7) Ineffective post-PTA adjuncts.
8) Progression of the native atherosclerotic process.

In the majority of clinical settings, the initial procedure restores an adequate lumen in more than 90% of the patients; however, a substantial number of these restenose in the next 6 - 12 months. Thus, 1 year following an initially successful *coronary angioplasty,* restenosis is a significant problem in 25 - 40% of the patients (1, 2, 3) - compare this with coronary bypass grafting surgery (using saphenous vein grafts) where there is a graft stenosis/occlusion rate of over 50% at 5 years (Fig 6.l). Even the use of stents has not made as big a dent in this problem as was originally expected, and the natural history of patients with in-stent restenosis is truly dismal, with postangioplasty restenosis rates ranging from 25 - 85% (depending on whether the restenosis is focal or diffuse).

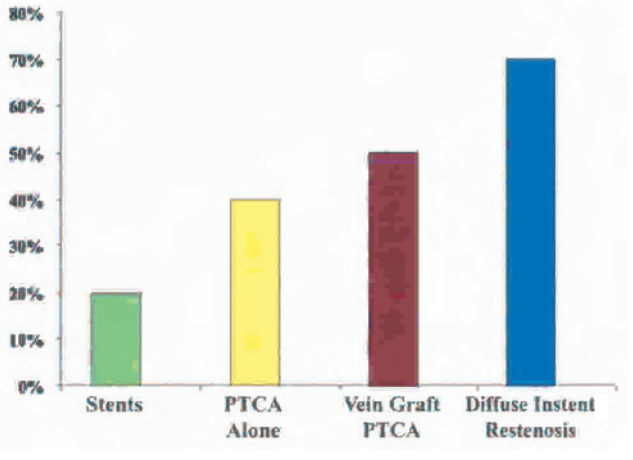


Figure 6.1 : Durability of Coronary Angioplasty

In other parts of the vasculature, the post-PTArestenosis rate varies markedly with the anatomic site. Apart from the factors enumerated above, in the lower extremity, the indication for the intervention (claudication vs. limb salvage) also seems to affect the restenosis rate. Thus, even *iliac angioplasty* - which is generally considered to have very durable results - can have a restenosis rate of 20% in the first year when done for total occlusions, with inadequate run-offs. When the indication for intervention is limb salvage, the results are even worse. Stenting has improved these numbers to some extent, but the situation is still far from ideal. Similarly, only about 60% of the *femoropopliteal angioplasties* are patent at 1 year when the procedure is performed for occluded vessels with a poor run-off (Fig 6.2). The length of the stenosis is another important prognostic factor - patients with narrowing extending over 7 cm do particularly poorly (4, 5). Blocks at or beyond the *popliteal trifurcation* do much worse, with a 2 year limb salvage rate of 60 - 80%. With longer follow-up, these figures look even more dismal.

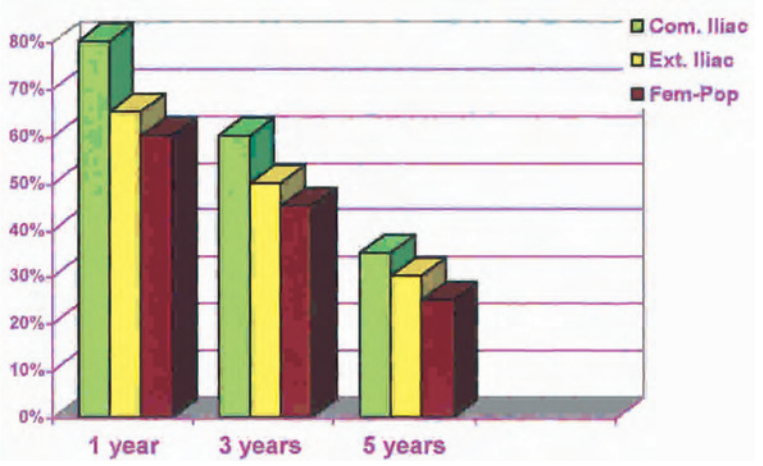


Figure 6.2 : Long-term results Following Angioplasty In The Ilio-femoral Vasculature

The situation is no different with the hemodialysis vascular accesses(Fig 6.3, 6.4). Though the initial patency rate with the Brescia-Cimino fistulas is very high and over 90% have a useful patency at 12 months, about a third of these occlude by four years. The situation with the PTFE grafts is even more problematic - most studies show a one year patency rate of about 60% but by two years, barely 40% are still functioning without any further intervention (6).

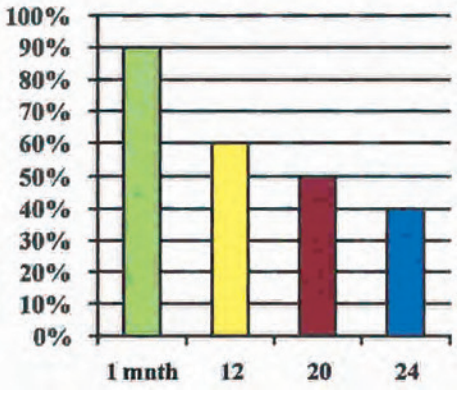


Figure 6.3 : Primary Patency of Dialysis Accesses

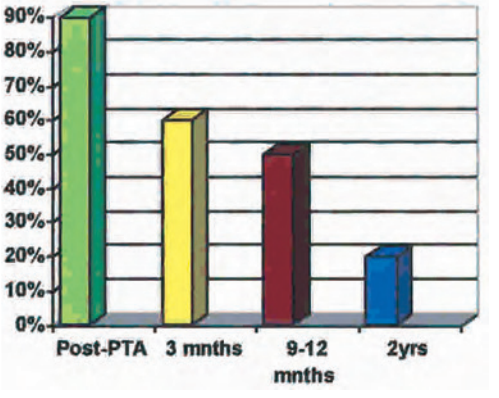


Figure 6.4 : Secondary Patency of Dialysis Accesses Following PTA

PROPOSED MECHANISMS FOR RESTENOSIS

Postangioplasty restenoses (PARS) complicates about one third of the cases of balloon angioplasty in medium and small arteries; most cases occur within the first year following the procedure. *Conceptually, restenosis can be considered a mechanism of vascular "healing" and "remodeling" that probably occurs to some degree in all cases.* Despite a multitude of different prognostic factors, the post-procedural minimal lumen diameter (MLD) has consistently been the most important predictor of late restenosis in several major trials (7). Serial angiographic studies have confirmed that most patients lose at least some of this initial luminal diameter gain over the next 6 - 12 months (”late loss”)(8). The absolute magnitude of this late loss is dependent on several patient, lesion and procedural factors and is normally distributed around a mean value of 0.37 - 0.50 mm (9); most importantly, this late loss is directly proportional to the acute gain that has been achieved. To better characterize this relationship, the parameter of late loss index has been devised. The arithmetic late loss index is determined by the late loss divided by the acute gain, while the regression late loss may be determined from the slope of the correlation between the late loss (y axis) and the acute gain (x axis). This has led to the "bigger is better" concept, which has been the driving force behind the development of numerous interventional devices. In fact, the whole spectrum of debulking devices and stents owe at least a part of their "success" to the larger "acute gain" that is obtained at the initial intervention.

ACUTE PARS:

Acute closures and reclosures are those that occur during or immediately after the PTA. Causes include spasm with or without thrombosis, dissection with complete closure, and elastic recoil. Thrombosis and dissection are really complications of PTA and occur in < 1 - 2% cases. In contrast to these, elastic recoil is an important determinant of the final luminal diameter. The dilated vessel, after a variable period of time that may range from minutes to days, loses a portion of the diameter gained from balloon dilatation. This loss is as a result of elastic recoil. Elastic recoil may be more important in eccentric lesions compared to concentric lesions, as the former has an uninvolved segment of vessel wall which can get stretched and subsequently undergo recoil. The total magnitude of this loss as a result of elastic recoil may be as much as 30% of the gain from balloon dilatation. Stents act as a rigid internal scaffold and completely eliminate this lumen loss.

Predictors of abrupt vessel closure

Preprocedure -

Clinical factors:	Female gender
	Unstable angina
	IDDM
	Inadequate anti-platelet therapy
Angiographic factors:	Thrombus
	> 90% stenosis
	Stenosis length > 2 luminal diameters
	Stenosis at branch point
	Stenosis at > 45 degree bend
	Right coronary artery stenosis

Postprocedure:

Intimal dissection > 10 mm
Residual stenosis > 50 %
Transient in-lab closure
Residual trans stenotic gradient > 20 mm Hg

DELAYED PARS:

Although elastic recoil may play some role, there is mounting evidence from animal models as well as human studies (angioscopy, study of materials obtained from atherectomies, and autopsy studies) that the most common mechanism of delayed PARS involves a combination of smooth muscle proliferation resulting in ***neointimal hyperplasia*** (NIH), and changes in the vessel wall circumference, or ***arterial remodeling.***

Neointimal Hyperplasia

Bromodeoxyuridine labeling have shown that 10 - 20% of medial smooth muscle cells begin to proliferate within 24 - 48 hrs. of balloon angioplasty (10, 11). After proliferating in the media, smooth muscle cells migrate to the intima at around 4 days, at which time some undergo further cycles of cell proliferation. In these models, although the cycle of medial proliferation, chemotaxis and intimal proliferation had occurred maximally by 1 week, progressive intimal thickening occurred for up to 8 weeks as a result of ongoing synthesis of connective tissue matrix and cellular hypertrophy (Figs 6.5, 6.6, 6.7).

Biological determinants of smooth muscle cell proliferation

The complex and multifocal processes regulating smooth muscle proliferation and migration are incompletely understood.

1) Role of vascular injury

Direct effects of vascular trauma: Vascular injury promotes smooth muscle cell proliferation by antagonizing the normal growth inhibitory processes of the undamaged arterial wall (12, 13, 14). In resting state, < 1 % of the medial smooth muscle cells are labeled with bromodeoxyuridine in normal artery segments, compared to 40 - 50% in damaged segments after balloon abrasion.

Numerous mechanisms can account for this:

a) Endothelial denudation as a result of the balloon angioplasty results in loss of growth-inhibitory heparin-like glycosaminoglycans.

b) The platelets that adhere to the area of "injury" release antiheparin factors such as platelet factor 4 and heparitinases which reverse the effects of heparin sulfates produced normally by the smooth muscle cells. These heparin sulfates are believed to be responsible for maintaining the smooth muscle cells in a nonproliferating state and contractile phenotype.

c) Several mitogens may also be released from the damaged endothelium as well as the smooth muscle cells.

Platelet-vessel wall interaction: Endothelial injury results in platelet adhesion. Shortly after the platelets adhere to the site of injury, they release all the contents of their alpha granules, including platelet-derived growth factor (PDGF), epidermal growth factor (EGF), beta-

transforming growth factor (beta-TGF), platelet factor 4, etc. Endothelial damage allows the heparin-neutralizing factors to penetrate the vessel wall. This releases the smooth muscle cells from growth inhibition and makes them susceptible to stimulation by PDGF. Once PDGF is bound to its receptor on the smooth muscle cell, the cell is able to enter the cell cycle; progression into the active phase of replication may depend on the synthesis of somatomedin-C by the smooth muscle cell itself. EGF and beta-TGF exert a synergistic effect on cellular proliferation. Smooth muscle cell proliferation continues beyond the phase of platelet deposition, suggesting that once the process is initiated, it can be perpetuated by other means. Migration of these cells to the intima is probably under the influence of PDGF which has chemotactic properties (15, 16, 17).

Finally, as a response to vascular injury and inflammation, aggregated lymphocytes may play a role in intimal proliferation by release of their cytokines like tumor necrosis factor (TNF), interleukins and beta-TGF.

2) Role of hemodynamic shear stress

The importance of normal fluid dynamics is illustrated by the observation that intimal hyperplasia is most prominent at bifurcations in cases of spontaneous atherosclerosis. Though there is some disagreement on the nature of the hemodynamic forces involved, there is a general consensus that intimal hyperplasia is most marked at sites of low and oscillatory shear stress. The mechanism of the "mitogenic" effect of low and oscillatory shear stress is unclear, but may involve impaired recovery of endothelial cell function after denudation (18 - 23). In applying this concept to clinical angioplasty, significant residual postangioplasty stenosis may be associated with elevated wall shear rates at the site of the lesion, favoring platelet deposition and thrombus formation, while the post-stenotic segment is an area of low or oscillatory stress, favoring intimal proliferation.

3) Role of thrombin

Pathologic and atherectomy specimens suggest that incorporation of thrombus into the atherosclerotic lesion plays a significant role in the restenotic process. Alpha-thrombin is believed to have an important role in the regulation of smooth muscle proliferation in response to vascular trauma (24 - 26). During thrombosis, thrombin gets tightly bound to the arterial extracellular matrix, where it can exert its effects for a prolonged time, protected from the inhibitory effects of anti-thrombin III. Thrombin is known to have mitogenic activity for fibroblasts as well as smooth muscle cells. It is a potent activator of multiple growth-related signals in smooth muscle cells, including expression of *c-fos* oncogene resulting in increased protein synthesis. In its various forms, it stimulates several intracellular events in common with other growth factors, including phosphoinositol hydrolysis, increased intracellular calcium concentration, and sodium influx. Thus, while the platelets may be important in the initiation, long term alterations of smooth muscle function and proliferation may be under the influence of thrombin and its derivatives.

4) Miscellaneous mechanisms

Numerous other factors/mechanisms may be operational in neointimal hyperplasia. Fibroblast growth factor and angiotensin II have been incriminated in smooth muscle hyperplasia. Angiotensin II seems to activate the protooncogene that is responsible for the transduction of mRNA in neointimal and vascular smooth muscle cells, and this mitogenic mechanism is activated within hours of balloon induced injury (27, 28).

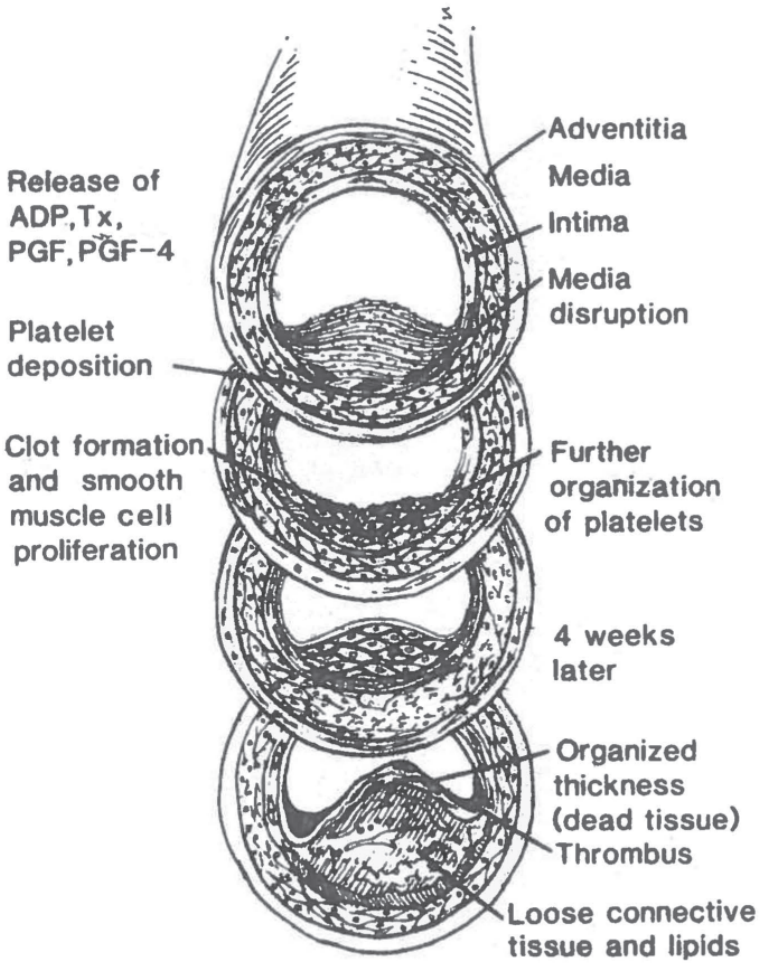


Figure 6.5 : Schematic representation of neointimal hyperplasia. From: Vliestra RE, Holmes DR, eds. PTCA - Percutaneous Transluminal Coronary Angioplasty. Philadelphia: FA Davis, 1987. Reproduced with the permission of the Mayo Foundation

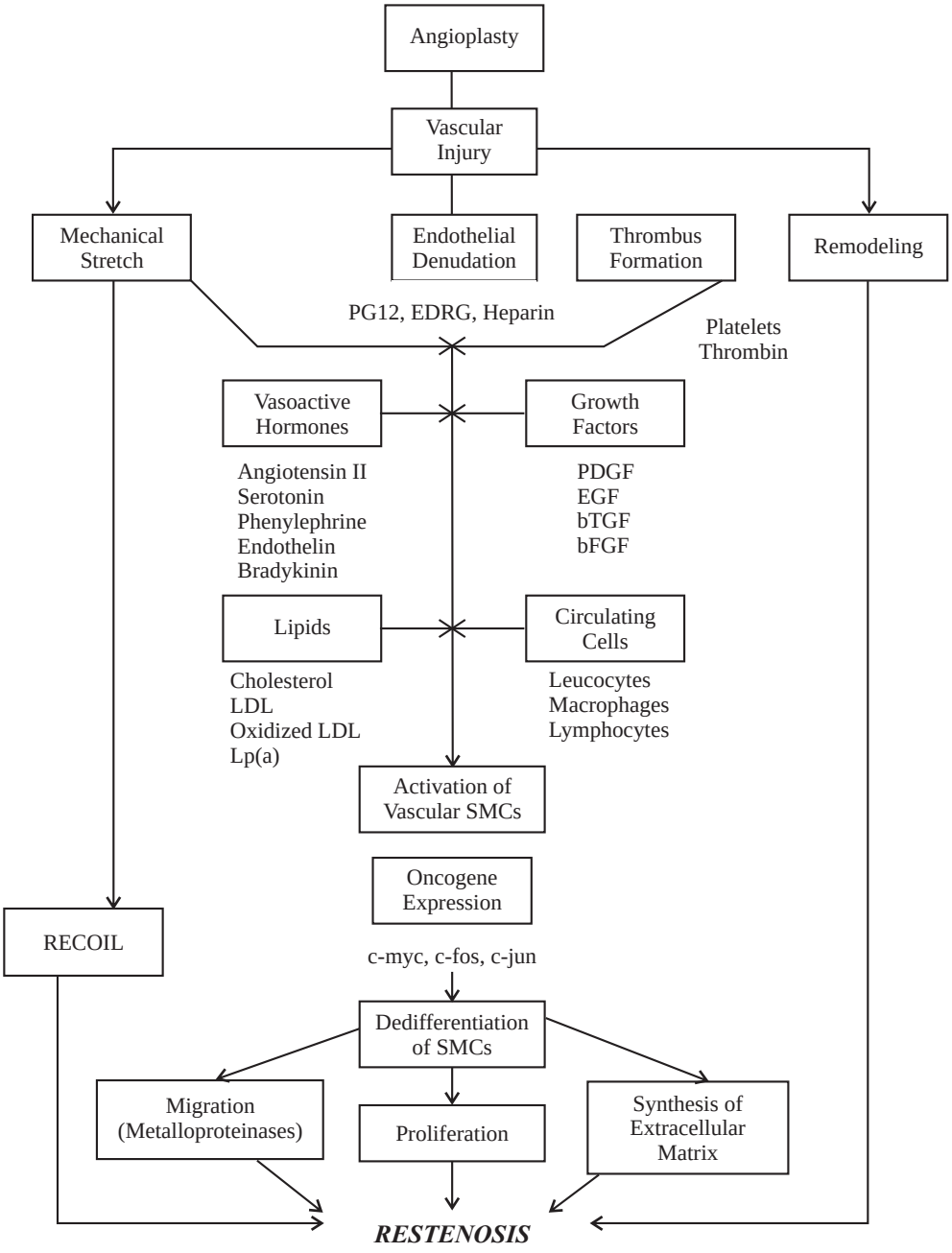


Figure 6.6 : Cascade of post-angioplasty stimuli resulting in restenosis. (From Serruys P, Kutryk M.Antirestenosis Alternatives For The New Millenium. In: Waksman R. ed. Vascular Brachytherapy, 2nd Ed.1999. Armonk, NY: Futura Publishing Company, with permission)

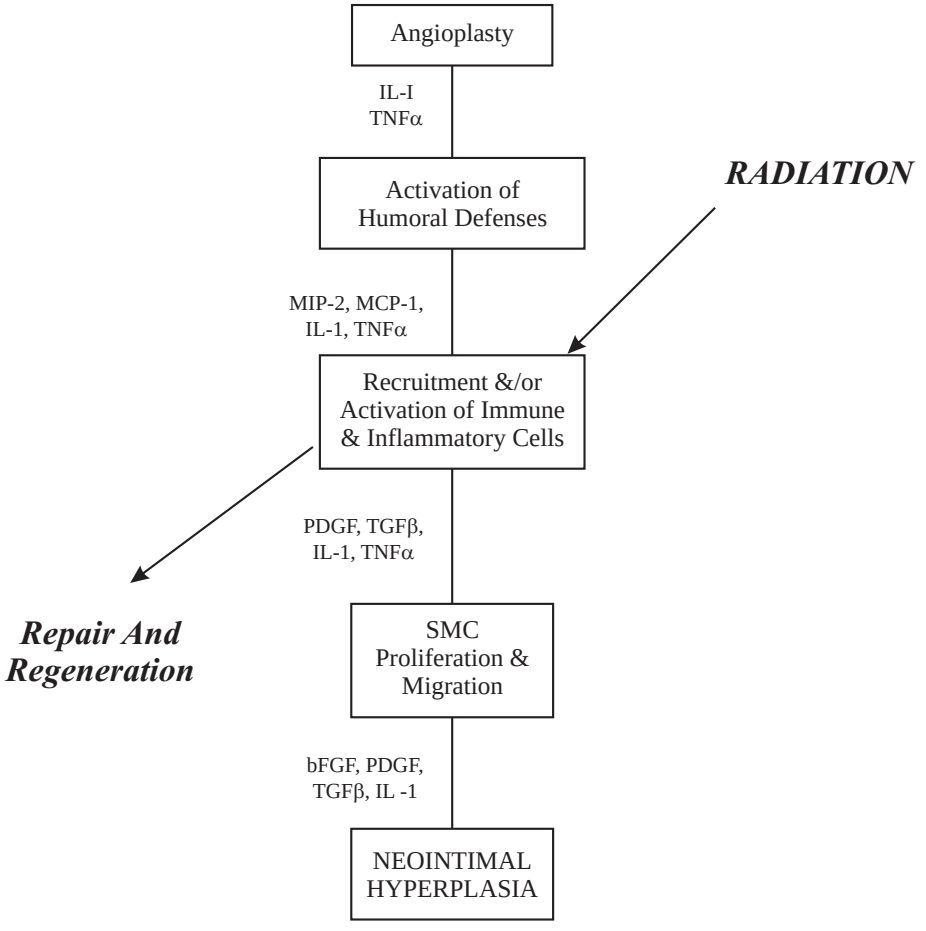
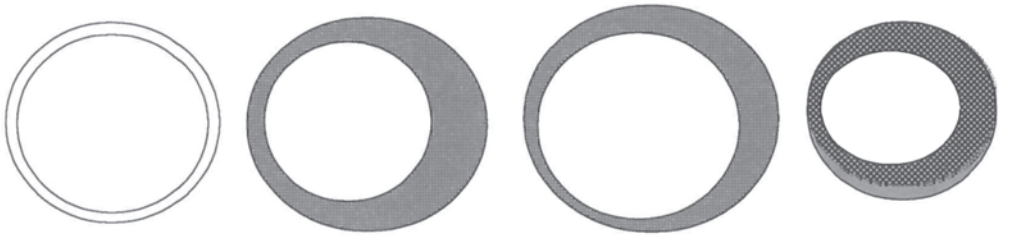


Figure 6.7 : Alternative Hypothesis With The Monocyte/Macrophage Playing A Central Role As The Source Of The Chemokines And Growth Factors (From Rubin P, Williams J, Finkelstein J et al. Radiation Inhibition versus Induction of Vascular Restenosis. In: Waksman R. ed. Vascular Brachytherapy, 2nd Ed. 1999. Armonk, NY: Futura Publishing Company, with permission.

Arterial Remodeling

This is the second important component of late PARS. Broadly speaking, all artery size changes following coronary angioplasty are included under the term "arterial remodeling". This has been referred to variously in the literature as compensatory enlargement, artery expansion, acute recoil, chronic recoil, chronic constriction, and arterial shrinkage. Essentially, following balloon angioplasty (and in response to neointimal hyperplasia), arteries can enlarge, contract or remain unchanged (29, 30). Arterial size changes may be *favorable* (adaptive) or *unfavorable* (pathological) in preserving the lumen size. *Perfect remodeling* occurs when an artery expands to equal or exceed the neointimal growth. Lumen size is unchanged and there is no angiographic restenosis. *Favorable remodeling* occurs when the arterial enlargement partially compensates for the neointimal thickness. Thus the decrease in lumen size due to neointima formation is incompletely compensated (but not eliminated) by some degree of arterial enlargement. Conversely, *unfavorable remodeling* occurs when the arterial wall contracts. This "contracture" potentiates the effect of any neointimal hyperplasia in causing angiographic restenosis (31).



"Normal" Artery	"Favorable" Remodeling (Arterial Wall Enlargement Partially Compensates For The Plaque)	"Positive" or "Perfect" Remodeling (Arterial Wall Enlargement Fully Compensates/Over Compensates For The Plaque	“Unfavorable" Remodeling (Arterial Wall "Contracture" Potentiates Effect Of The Plaque

Figure 6.8: Examples of arterial remodeling

With the availability of Intravascular Ultrasound, the total arterial cross-sectional area is easily estimated by measuring the external elastic lamina cross-sectional area (which is a *very* reproducible measure). Using this measure, the occurrence of the remodeling phenomenon has been confirmed in the OARS (Optimal Atherectomy Restenosis Study) trial (32), while the time course of remodeling was studied in detail in the SURE (Serial Ultrasound analysis of Restenosis) trial (33). The latter trial showed that there was little change in the external elastic lamina cross-sectional area within the first 24 hours following angioplasty. Early adaptive remodeling (an increase in the external elastic lamina cross-sectional area) occurs between 24 hours and 1 month, while late pathological remodeling (decrease in external elastic lamina cross-sectional area) occurs between one and six months. Although several mechanisms have been proposed to explain this phenomenon of remodeling, the exact pathogenesis is unclear. It is very likely that the process is akin to that of wound contraction. The adventitia probably plays a key role in this through an accumulation of alpha smooth muscle actin positive myofibroblasts which can cause constriction of the external elastic lamina.

IN SUMMARY

A number of mechanisms are involved in the processes following angioplasty. Collectively, they constitute the "response to injury", and are required to heal the balloon-induced injury to the vessel wall. When healing occurs in a controlled manner, the vessel wall is remodeled with an enlarged lumen. When the healing process is uncontrolled, and marked by a proliferative response, the hyperplastic lesion of restenosis results. Superimposed on this intimal hyperplasia is the variable component of elastic recoil and late vascular remodeling and the unpredictable course of the native atherosclerotic plaque. *Though the situation is never quite dichotomous, the IVUS data seems to indicate that the majority of the restenosis after balloon angioplasty alone is due to negative arterial remodeling, which can be effectively counteracted by deploying a stent; conversely, the restenosis after stent implantation is primarily due to tissue overgrowth as a result of neointimal hyperplasia (in-stent restenosis). This may provide us with some insights into the possible approaches that may prove useful in preventing post-angioplasty restenosis.*

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7

Insights From Intravascular Ultrasound

Angiography is currently, and will probably remain, the gold standard for vascular evaluation. However, discrepancies between pathological specimens and angiographic findings have long been recognized. The basic limitation of angiography is that it does NOT image the blood vessel; it only provides two-dimensional (2-D) longitudinal images of patent vessel lumens. It provides no information regarding the structure of the vessel wall, plaque morphology or composition, etiology of stenoses, occlusions or perivascular structures. Angioscopy allows direct visualization of the vessel lumen but is technically challenging and, once again, provides no cross-sectional information. Intravascular ultrasound (lVUS), on the other hand, provides very good cross-sectional images, allows a detailed evaluation of the diseased vessel wall, gives a good assessment of the various endovascular interventions, and allows one to make precise cross-sectional measurements. Because of these advantages, IVUS has become a very useful imaging device during both coronary and peripheral interventions. The development of user friendly and reliable IVUS units has led to a significant expansion of the role of IVUS during percutaneous vascular interventions (1).

The importance of IVUS in endovascular brachytherapy stems from its ability to provide crosssectional images, and information regarding plaque morphology and distribution. This may allow for appropriate isotope selection, precise dose prescription and accurate post-treatment dosimetry. It also offers the potential for real time 3-D treatment planning in the cardiac catheterization laboratory by incorporating parameters such as non-centering, plaque distribution (in longitudinal and circumferential directions), and inhomogeneity corrections (for stents and various plaque compositions).

There are two basic types of ultrasound transducers used with IVUS. *Phased array transducers* rely on multiple crystals, usually 64, arranged in a circumferential manner around the catheter tip. This annular array design may be mounted on relatively small catheter shafts (< 5F) and allows for over-the-wire catheters. These catheters tend to be flexible and thus are optimal for passage into tortuous vessels or small vessels such as coronary arteries. *Mechanical transducers* use a rotating transducer (1600 - 180 rpm) powered by an external mechanical motor drive. Typically, the ultrasound beam is aimed toward the hub of the catheter. The beam is then reflected onto a rotating mirror that allows for the creation of a 360-degree image. Mechanical transducer designs tend to require more rigid catheters because the drive shaft tends to be fairly rigid. The IVUS catheters can be connected to an automated pull-back system which provides for a motorized pullback at a fixed speed.

IVUS systems are plagued by several image artifacts. An artifact common to both systems is the *ring-down artifact*. This is a bright halo of variable thickness surrounding the catheter. It is caused by transducer oscillation filling the area immediately adjacent to the catheter with noise,

segments of the coronary artery, the collagen content in media is particularly high and the echogenicity of the media increases; this layer blends into the intima. In young patients the intimal thickness can be less than the practical axial resolving power such that there may not be sufficient overall tissue thickness to register as a separate layer on the IVUS scan. Additionally, the media may be so thin, especially in advanced stages of coronary artery disease, that it may appear entirely absent (5, 6).

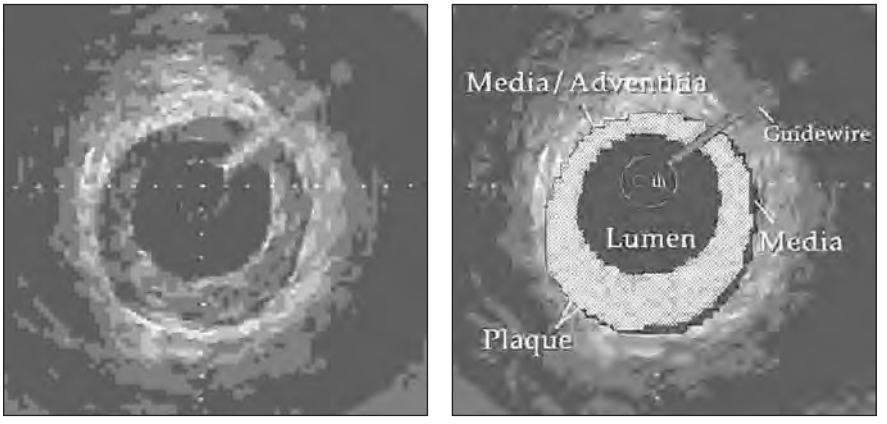

Figure 7.1 : Cross-sectional format of a typical intravascular ultrasound image. Cath indicates the imaging catheter. The ultrasound reflection from the guidewire is shown at 2 o' clock. In this image, the media is seen as a well-defined, dark band between 1 and 6 o' clock; elsewhere the media is less distinct but the media/adventitia interface is still clear. Calibration dots are 0.5 mm apart. From: Yock PG, Fitzgerald PJ: Intravascular Ultrasound Imaging. In: Baim DS, Grossman W (eds) Cardiac Catheterization, Angiography and Intervention, 5th Ed. Baltimore, Williams and Wilkins, 1996. With permission.

Blood

Generally, blood is easily recognized on IVUS images by a characteristic speckled pattern that is constantly changing with systolic and diastolic blood flow, being slightly more echogenic in systole. Sometimes, however, when blood flow is slow or stagnant (such as proximal to a

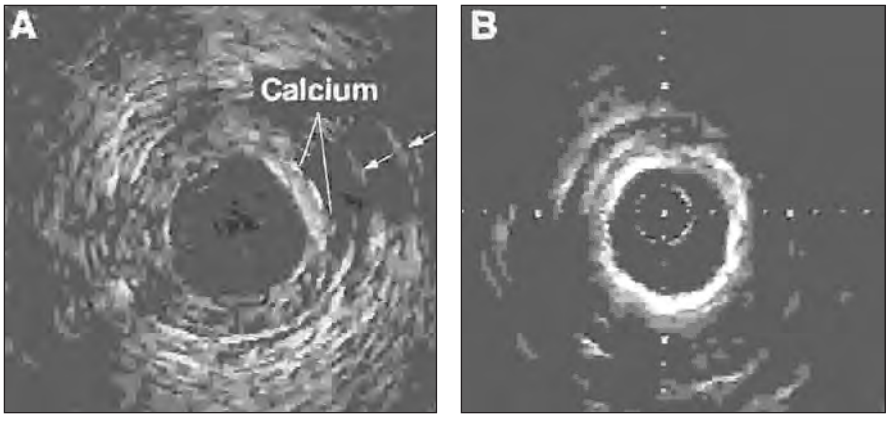

Figure 7.2: Two examples of calcific plaque. (A) A small arc of calcium is centered at 2 o' clock. Note the shadowing and the reverberations (concentric arcs beyond the calcium). (B) A complete ring of calcification at the luminal surface. From: Yock PG, Fitzgerald PJ: Intravascular Ultrasound Imaging. In: Baim DS, Grossman W (eds) Cardiac Catheterization, Angiography and Intervention, 5th Ed. Baltimore, Williams and Wilkins, 1996. With permission.

making this area unavailable for imaging. Another problem associated mainly with mechanical catheters is *nonuniform rotational distortion (NURD)*. When the rotating transducer inside the ultrasound catheter is exposed to frictional forces (i.e., bending of the catheter, a too tight hemostatic valve), portions of the images are stretched or compacted. Manipulations of the catheter can usually eliminate this artifact. In tortuous or calcified arteries, however, NURD may be severe and less easily corrected (2). Image quality can also be affected by catheter position. The ultrasound catheter usually lies off-center within the coronary artery lumen. This results in the vessel structures nearest to the catheter appearing significantly brighter than those on the opposite side; this may cause misinterpretation of plaque composition. Also, the artery wall closest to the catheter near field is most affected by the ring-down artifact and can occasionally make correct interpretation of the luminal border difficult. In larger vessels or at the ostium of a vessel, off-axis position of the catheter may alter vessel geometry in an elliptic fashion and artificially increase lumen and vessel area. In most coronary artery studies, this effect seems to be relatively small (3). Mechanical catheters also experience image degradation due to *ghost images*, when structures of high echogenicity such as calcium or metal struts of coronary stents are imaged. These images appear on the side of the transducer that is opposite to the bright structure being imaged and are due to reflections of high intensity that are received in the back of the transducer, resulting in a less intense copy of the true image being represented on the opposite side of the catheter at an equal distance. Finally, difficulties in location of the true interface may occur in regions of eccentric catheter position in the vessel lumen; the intima may appear fragmented and, in cases of stent deployment, the metal struts appear oblique and stretched, spreading into the lumen. This phenomenon is caused by limitations in lateral impulse response and correlation of these morphologic observations with the changes in catheter position during the cardiac cycle may help clarify the issue.

More recently, systems have been designed in which the IVUS image is acquired by random scanning motion of a single transducer with computerized image reconstruction. Three dimensional (3-D) computer enhanced reconstruction of IVUS images is also achievable. The 3-D images are obtained by performing a slow pull back of the IVUS catheter at a uniform speed. The 3-D images are obtained on line during the procedure with minimal delay from the time of the pull back. This added information provides further insight into vessel wall, plaque, and lumen characteristics. Recently, a new forward-viewing IVUS catheter has been described that provides rapid 3-D reconstruction (4).

Endovascular Anatomy (2)

Arterial Wall

A typical IVUS image of a coronary arterial segment shows a three-layered wall structure (Fig. 7.1). The inner layer is relatively bright compared to the blood surrounding the catheter and represents the intima and internal elastic lamina, including plaque in diseased arteries. The middle layer is the dark echo lucent medial stripe. The outer layer is quite echogenic (bright) and represents the external elastic lamina, adventitia, and periadventitial tissue. The reason for the different echogenic qualities of these wall components is mostly due to the relative amount of collagen and elastin. The reflectance of collagen is 1000 times greater than that of smooth muscle. Adventitia is rich in collagen and is therefore echoreflective, whereas media of coronary arteries contains mostly smooth muscle cells and is relatively echo lucent. Distinct separation between the intimal and medial layers on IVUS can sometimes be difficult. Thus, in the proximal

severe stenosis that is occluded by the ultrasound catheter), this lumen/intima border can be difficult to distinguish. In this situation, RBC rouleaux formation gives rise to a very significant increase in backscatter. A saline flush can clear the lumen temporarily and help to identify the presence of stagnant blood on the IVUS image

Calcific Plaque

lVUS provides important information about plaque composition (7, 8). Calcific plaque is characterized by a bright reflection with intense signal attenuation and shadowing beyond. Another feature of calcification is bright, concentric ghost arcs or reverberations that extend beyond the calcific structure within the shadowing. Reverberations are caused by repeated reflection of the echo signal from the transducer and the calcific plaque, resulting in a multiplication of the echo (Fig.7.2). In certain cases, shadowing may be present on the ultrasound scan without any evidence of bright tissue reflections typical of calcific deposits in the imaged plane. Movement of the catheter a short distance forward or backward often reveals the calcification to be just out of plane. Acoustic shadowing also occurs in the absence of calcium in the presence of dense fibrous tissue. Thus, it is probably more appropriate to refer to lesions with shadowing on IVUS as fibrocalcific.

Fibrous Plaques

These plaque types are usually recognized by an overall echogenicity that is less bright than that from calcium but higher than that from muscle or fat tissue; the brightness of fibrous tissue is similar to that of adventitia. Because fibrous tissue has a higher content of collagen and elastin, it can markedly attenuate the signal as it interrogates the plaque substance. However, this is a progressive attenuation (in contrast to the abrupt attenuation caused by calcium), and a shadow may be produced in the distal field, but no reverberations are observed (Fig. 7.3). In casual description of IVUS images, plaque is commonly divided into hard and soft, referring to the presence or absence of shadowing. While this classification does not represent an accurate pathologic description because soft plaque would be firm to the touch (9), it does provide a convenient shorthand description of the gray-scale speckle characteristics.

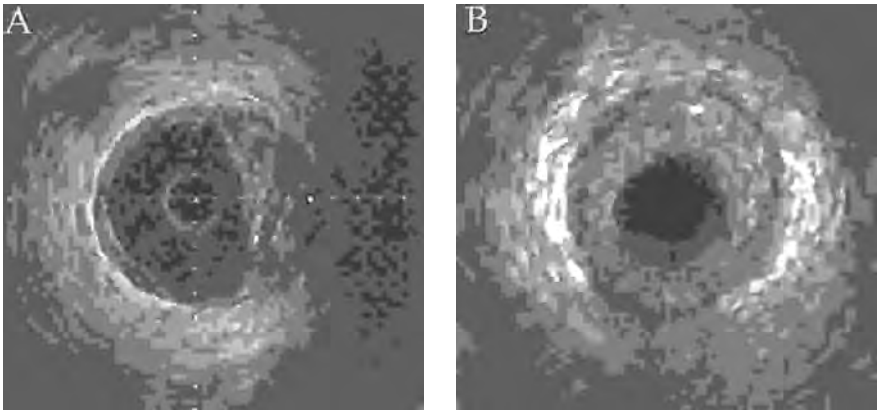

Figure 7.3 Eccentric (A) Vs concentric (B) plaque accumulations. In (A) there is a deep plaque between 12 and 5 o'clock, with relatively normal wall elsewhere. In (B) the plaque is distributed nearly equally around the vessel cross-section. From: Yock PG, Fitzgerald PJ: Intravascular Ultrasound Imaging. In: Baim DS, Grossman W (eds) Cardiac Catheterization, Angiography and Intervention, 5th Ed. Baltimore, Williams and Wilkins, 1996. With permission.

Fatty Plaque

Fatty plaque is relatively echolucent and has a soft gray-scale appearance on the IVUS image. Its homogeneous structure permits the ultrasound signal to travel through the tissue without encountering areas of high impedance mismatch. Consequently the ultrasound beam is less attenuated than, for example, in fibrous plaque, resulting in improved visualization of the surrounding adventitial tissue and perivascular structures. Occasionally, echolucent areas within fibrous plaque can be identified and probably represent accumulations of lipid. Analysis of integrated back-scatter and higher-order statistical functions based on the radio frequency signal may allow more detailed analysis in the future (10).

Plaque Distribution and Remodeling

On IVUS examination of angiographically normal-looking arterial segments, some degree of plaque can be appreciated throughout the coronary artery. By angiography, a target lesion is usually referenced to the most normal-looking adjacent reference segment. IVUS usually reveals that the average reference segment is occupied by a plaque burden of 35% to 40% (11). One reason this disease is not appreciated on a routine angiogram is the normal compensatory remodeling of the vessel wall in response to the early plaque. This preserves the lumen diameter, with a resultant "normal" angiogram (underscoring the concept that an angiogram is actually a

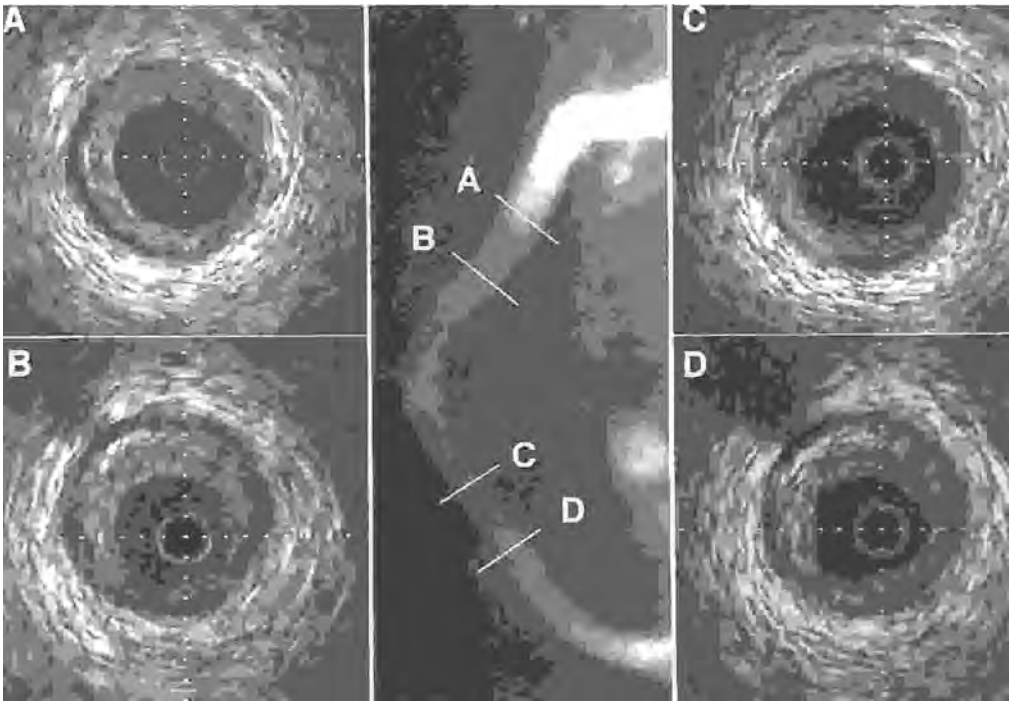

Figure 7.4: Angiographically silent disease. The angiogram of the right coronary artery in the middle panel suggests minimal disease. However, the four ultrasound images, taken at the scan planes indicated on the angiogram, show significant circumferential accumulation of plaque ranging from 0.5 to 1.5 mm thickness. In each image, the lumen is fairly large, round and regular, accounting for the benign angiographic appearance. From: Yock PG, Fitzgerald PJ: Intravascular Ultrasound Imaging. In: Baim DS, Grossman W (eds) Cardiac Catheterization, Angiography and Intervention, 5th Ed. Baltimore, Williams and Wilkins, 1996. With permission.

"luminogram") - Fig. 7.4. Eventually, this mechanism is exhausted (after approximately 40% of the lumen is occupied by plaque), and further plaque growth results in encroachment on the lumen and angiographic disease detection. In some arterial segments, instead of vessel expansion, vessel shrinkage may occur, which has been referred to as unfavorable or negative remodeling. This process is often observed as part of the restenosis process following coronary arterial wall injury post-intervention. The exact cause for the variability in the remodeling responses remains to be elucidated.

With respect to the topography of plaque distribution, lVUS provides direct evidence supporting the relationship between shear stress and plaque growth. Changes in shear stress because of flow separation and reattachment zones and changes in vessel wall geometry contribute to the preferred development of plaque at or near branch points in the coronary vasculature. Similarly, the maximum atheroma mass in the proximal LAD is observed to be opposite to the takeoff of the circumflex artery, with relative sparing of the flow divider segments. IVUS can also provide information about entities such as a thrombus, aneurysm, dissections, hematomas, etc.

Quantitative Coronary Ultrasound (2)

Because of its cross-sectional nature and relatively high resolution, quantitative coronary ultrasound (QCU) is generally more accurate than quantitative coronary angiography. Area calculations are also less sensitive to manual errors than diameter determinations, and crosssectional area is a relatively straightforward parameter that is more reliable, reproducible, and physiologically relevant than vessel diameter because it represents the entire cross section. Additionally, QCU provides the opportunity to measure plaque area and thus to estimate plaque volume within the target segment. Best of all, this information is available in real-time. The basic principle of measurement in QCU is planimetry. Lumen/intima and media/adventitia borders (the external elastic lamina - EEL) are traced manually followed computerized calculation of lumen and cross-sectional vessel area. The area enclosed by the EEL comprises the vessel area, while the area enclosed by the lumen/intima is the lumen area. The area enclosed between the intimal surface and the adventitia (vessel area minus lumen area) represents the plaque area + the media area. The media is included in this measurement because a) the media is not always distinguished as a clear layer, and b) the media can appear erroneously thin on IVUS images because of an effect called blooming. This effect is caused by the transition of the ultrasound signal from a region of high (intimal plaque) to low (media) reflectivity, resulting in a spreading of the signal into the medial area. The intima may therefore appear thicker at expense of the media.

Typical QCU parameters include minimum and maximum lumen and vessel diameter, their ratio (i.e., minimum lumen diameter divided by the maximum lumen diameter), and the eccentricity ratio of the minimum plaque thickness to the maximum plaque thickness. As in quantitative coronary angiography, coronary target lesions are usually compared to a reference segment that needs to be chosen by the operator. Typically the most normal-looking vessel segments proximal and distal to the target site are measured and averaged for comparison with the lesion. The distance between stenosis and reference segment should be less than 10 rum, and there should be no major side branch exiting from the vessel of interest to avoid anatomic influences on volume changes.

Applications

IVUS allows transmural, tomographic imaging of coronary arteries in vivo, providing unique insights into the pathology of coronary artery disease. Because it defines vessel wall geometry in a manner not possible with any other imaging modality, IVUS plays a major role in the postprocedure evaluation following a PTCA. Initially, sequential (pre-intervention and post-intervention) IVUS studies were used to study mechanisms of angioplasty devices including balloon angioplasty, directional coronary atherectomy, high speed rotational atherectomy and excimer laser coronary angioplasty. Later the role of IVUS was expanded to study the mechanism of restenosis. IVUS allowed for the separate assessment of the contribution of tissue removal/ablation and that of vessel expansion to the final lumen enlargement achieved (12). Based on these studies, restenosis, or late lumen loss, can be subdivided into two distinct underlying processes: tissue proliferation and arterial remodeling. Histologic studies have shown that the external elastic membrane cross-sectional area, as measured by IVUS, is a reproducible measure of the total arterial cross-sectional area. Similarly, while IVUS cannot accurately measure media thickness, the plaque + media cross-sectional area (calculated as the external elastic lamina crosssectional area minus the luminal cross-sectional area) is useful as a measure of the plaque mass. Arterial remodeling, therefore, can be measured as a change in the external elastic membrane cross-sectional area, while tissue proliferation can be estimated by the change in plaque + media cross-sectional area.

Thus, IVUS may be used as an adjunct to conventional imaging to enhance diagnostic infonnation, as an adjunct to complex interventional procedures to provide an insight into changes in plaque and changes in vessel wall after interventions, as a primary imaging modality to guide and monitor interventions in a real time fashion (size vessel lumen, ensure stent apposition, etc), and potentially as a therapeutic tool using ultrasound echoes to alter or fragment plaque or thrombus.

In the setting of endovascular brachytherapy, IVUS allows identification of the various layers of the vessel. This allows the radiation oncologist to determine the precise depth from the central catheter to which the dose should be prescribed (image- or target-based brachytherapy). This becomes especially important with b-emitters where there is a very rapid fall-off in dose with increasing depth. Also, because of large and eccentric plaques, the catheter often occupies a rather eccentric position within the vessel lumen. This can result in a different sectors having a considerable heterogeneity in dose-distribution across the vessel wall. Images obtained with IVUS allow for accurate assessment of the dose-distribution, thus ensuring that there is no underdosing in the sector with the thickest plaque, while the relatively unaffected sectors are not overdosed. IVUS also allows for qualitative evaluation of plaque composition, which may have important implications for isotope selection and dose prescription.

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8

Rationale For Use Of Radiation Therapy To Prevent Post-Angioplasty Restenosis

Given the magnitude of the problem, a large number of therapeutic approaches have been used to try and modify the restenosis process. Unfortunately, despite over 55 trials involving more than 15,000 patients no adjuvant therapy has proven to be of consistent benefit, when used on a large scale. These approaches can be divided into mechanical and pharmacological:

Mechanical approaches

The principal goals of these techniques have been to create a larger and smoother lumen (i.e. a larger acute gain) and to minimize the associated damage, in an effort to reduce the stimuli for smooth muscle proliferation & thrombus formation.

These approaches include the use of *lasers* for plaque ablation & various *atherectomy devices* (directional and rotational) for plaque removal-debridement. The basic principle is to obtain a postintervention lumen that is as large and as smooth as possible, thus attempting to minimize the stimuli to neointimal hyperplasia, while "compensating" for some of the inevitable late loss. These debulking devices are quite useful in recanalizing difficult lesions; unfortunately, their impact on preventing subsequent restenosis is quite limited. Stents, on the other hand, not only help in obtaining a larger acute gain, but also playa pivotal role in the *maintenance of vascular patency*. This has given rise to a "stent mania", driven by an appreciation of the power of stenting to achieve superb hemodynamic acute angiographic and hemodynamic results in simple and complex lesions and the improved long-term outcomes. Stents achieve this by acting as an internal scaffolding - this helps "seal off' acute dissections, overcomes acute elastic recoil and maintains the enlarged vascular diameter by opposing any element of late remodeling or vascular contraction. Unfortunately, this is achieved at the price of an increase in neointima formation, and there are several subgroups of patients who continue to do poorly despite the use of stents. Thus, high rates of restenosis are still seen in restenotic lesions, saphenous vein grafts and ostial lesions. In-stent restenosis is a particularly difficult problem and the long term outcome of repeat interventions in this subgroup is quite unfavorable with recurrence rates of up to 80%.

Pharmacological approaches

Past experience

This includes the use of *anti-platelet* agents like aspirin, dipyridamole, ticlopidine, ciprostene and ibuprofen (1, 2,3,4). Heparin and warfarin have also been tried as *anticoagulants* with little success (5, 6). *Omega-3 fatty acids*, found in salt-water fish have platelet inhibitory and antiinflammatory properties, but clinical data concerning their efficacy in preventing restenosis is mixed (7). *Vasodilators* like nitroglycerin, calcium channel blockers, *serotonin antagonists*

like ketanserin, and *beta-blockers* have also been tried, without success. *Corticosteroids*, with their well known anti-inflammatory properties, have been assessed in at least three trials with no evidence of any benefit (8).

Present directions

Anti-thrombotic approach - This includes the evaluation of monoclonal antibodies to glycoprotein IIb/IIIa, or the von Willebrand factor, to prevent platelet adhesion to the damaged vessel wall (9, 10). Another approach utilizes *specific inhibitors of thrombin like* recombinant hirudin, etc (11).

Anti-proliferative approach - With the appreciation that post-PTA restenosis is essentially a growth disorder, it is obvious why most of the traditional anti-restenosis approaches failed. However, this new paradigm has led to the evaluation of several novel anti-proliferative therapies for the inhibition of neointimal hyperplasia. *Glucocorticoids* were the first such agent to be tried, with little success. Current studies are aimed at the potential use of *angiotensin-converting enzyme inhibitors*, as well as specific anti-PDGF agents, like tyrphostins (inhibitors of protein tyrosine kinase) and triazolopyrimidine (12).

Cardiologists, frustrated with the relentless, and potentially life-threatening nature of coronary restenosis, have labeled some of these as *"malignant restenosis"* and approaches similar to those in neoplastic disorders have been tried. These include colchicine (14) and *local, intramural methotrexate* (15), but neither of these have been clinically useful. Newer trials are evaluating the use of the *stent as a drug-delivery platform,* incorporating anti-neoplastic agents like *paclitaxel* and *rapamycin*. The technology required to transfer *anti-sense oligonucleotides* or protein products directly to the site of stenosis during angioplasty is also available. Its feasibility has been demonstrated in animal models. This approach is novel and holds great promise, but has yet to be translated to the clinical setting.

The most successful anti-proliferative therapy to date has been the use of ionizing radiation. The effects of ionizing radiation on proliferating tissues are well known. It is generally accepted that nuclear DNA is the target for ionizing radiation. However, therapeutic doses of radiation rarely cause DNA damage that is sufficient to affect the metabolic functions of the cell. The main effect of clinical doses of ionizing radiation is to impair the reproductive integrity of cells, especially in the rapidly proliferating tissues. As a consequence of this DNA damage, the cell dies when it attempts to divide. This effect of radiation on proliferating tissues has been clinically exploited to treat a variety of benign conditions characterized by uncontrolled proliferation. Relatively low doses, in one or more fractions, have been very effective in inhibiting non-neoplastic hyperplasia of mesenchymal tissues. Thus, keloids, which are benign dermal "tumors", arise from abnormal wound healing in genetically susceptible patients. They have reduced growth factor requirements in cell cultures and respond differently from normal skin to exogenous growth factors. These differences are attributed to the autocrine production of growth factors by the dermal cells, reduced production of growth-inhibitory peptides or alterations in growth factor receptor activity or postreceptor signal transduction (16). Kovalic et al (17) reported a twenty year experience with radiation therapy for preventing keloid formation. With a dose of 12 Gy, they were able to achieve a 73% recurrence free rate at a mean follow-up of 10 years. Similarly, heterotopic bone formation (occurring due to the migration & proliferation of pluripotent mesenchymal cells, with subsequent differentiation into osteoblasts), has been effectively controlled by doses of 7 - 10 Gy (18). Pterygium excision is associated with a

recurrence rate of almost 30%. Radiation, in doses ranging from 20 Gy to 50 Gy (in different fractionation schemes), has reduced this relapse rate to less than 10% (19). Radiation therapy is also used to treat a number of other benign or non-neoplastic conditions. These include exophthalmos, orbital pseudotumor, plantar warts, keratoacanthomas, hemangiomas, desmoids & fibromatoses, Peyronie's disease, ameloblastomas, aneurysmal bone cysts, gynecomastia, etc.(19).

Evidence Of Efficacy Of Ionising Radiation In Inhibiting Neoinitimal Hyperplasia

As discussed previously, vascular smooth muscle does not normally have a hierarchical organization and lacks an actively multiplying cell subpopulation. However, mechanical injury or other stimuli can alter the phenotype of these cells. The bromodeoxyuridine studies suggest that they undergo a change from a quiescent, contractile phenotype to one characterized by active proliferation, migration and matrix synthesis (20, 21). It follows that ionizing radiation could be effective in inhibiting this hyperplastic response, and preventing neointimal hyperplasia and subsequent restenoses.

In Vitro Work

SMCs and endothelial cells are not in a proliferative state under normal conditions and are hence relatively "radioresistant". However, proliferating, non-confluent explants of primate and rabbit aortic media showed a dose-dependent reduction in H-3 *thymidine incorporation* at doses from 100 - 3000 cGy without alterations in cell migration (22). Similarly, *cell survival studies on* exponentially growing rat aortic SMCs show them to be moderately radio-sensitive, with a D_o value of 120 - 160 cGy and extrapolation numbers of 2 - 10 (23). Fischell et al studied the effects of titanium wires impregnated with P-32 on rat and human aortic SMCs and cultured bovine aortic endothelial cells. There was a distinct 5.5 - 10.6 mm zone of complete SMC inhibition with activities as low as 0.006 microCi (24). These studies indicate that the SMC is not a particularly radioresistant cell, as was previously thought, and conventional doses of ionizing radiation can be quite effective in inhibiting SMC proliferation.

Animal Experimentation

Numerous animal studies attest to the efficacy of ionizing radiation in inhibiting intimal hyperplasia following arterial injury. Different animal models of angioplasty incorporate one or more features of the clinical scenario, but none offers perfect similitude. Diet-induced atherosclerosis in animals and early atherosclerosis in humans is typically lipid-rich; however, high-grade chronic coronary obstructions in humans usually contain large amounts of both collagen and calcium, and relatively little lipid. Collagen and calcium are deposited into and removed from plaques much slower than lipid. Because of these features, no one animal model completely simulates the vascular healing processes following catheter-induced trauma. Most animal models of restenosis occur in the absence of underlying chronic atherosclerosis with its associated pathobiology and flow abnormalities, and the lumen compromise is typically mild. Thus it has been suggested that the term animal model be replaced by animal preparation (25).

One of the earlier and more commonly employed models is the *rat carotid artery*(26). This is injured by deendothelialization and overstretch using an embolectomy catheter. Though this is

a relatively simple and inexpensive model, it suffers from 2 major limitations. It does not incorporate several histopathological features of balloon angioplasty in humans, especially medial dissection injury, separation of arterial layers and hemorrhage within the dissection planes. Also, the carotid artery is an elastic artery and many workers have questioned the relevance of changes in such an artery to the pathophysiology of a muscular coronary artery.

The *atherosclerotic rabbit iliac artery* is another commonly used model (27). Atherosclerotic lesions are induced by an initial balloon deendothelialization via the femoral artery, along with diet-induced hypercholesterolemia. Stenotic lesions, mimicing human atherosclerotic lesions, are formed after several weeks. These are amenable to balloon dilatation via the carotid artery underfluoroscopic guidance. The restenotic lesions are somewhat difficult to distinguish from the underlying atheroma, having a similar macrophage-foam cell-rich composition, unlike the exclusively SMC populace of the human restenotic tissue. Nevertheless, this model, like the rat model described above, has been proven useful in understanding the mechanisms of restenosis, and in evaluating anti-restenosis compounds.

The healing response to *balloon overstretch injury in the normal coronary arteries of the juvenile pig* is probably the most frequently used model today (28). These animals have a cardiac and coronary anatomy, and collateral circulation very similar to that in humans, and also have a closer phylogenetic proximity to humans. They also exhibit a substantial intimal proliferative response to coronary injury, unlike other large species like the dog. In the standard model, the tunica media is ruptured by dilatation with an oversized balloon, and the proliferative response is believed to be a function of the extent of this medial fracture. *Oversized stent placement in pig coronary arteries* has also been used as a model of restenosis (29). Neointimal lesions resulting from this injury are substantially more exuberant than the balloon-induced lesions. The healing response also shows some differences: a greater thrombotic response, more inflammation and inhibition of chronic constriction (or negative remodeling).

Regardless of the model employed, assessments of response to therapy have to be controlled for the degree of vessel injury (Table 1). One way of doing this is by expressing the final pathological result as a ratio of the intimal area to the length of the EEL fracture (lA/FL ratio).

Table 1 : Vessel Injury Score

(Schwartz R, Huber K, Murphy J et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am ColI Cardiol 1992;19:267-274)

Assigned Weight	Injury
0	Endothelium denuded: IEL intact; media may be compressed
1	IEL lacerated; media compressed. but not lacerated
2	I EL lacerated; visible lacerations within the media; EEL intact but may be compressed
3	IEL lacerated; deep medial lacerations extending through the EEL: stent coils may be found residing within the adventitia

External Beam Studies

Shefer et al (30) used high energy beta radiation from a sealed Sr-89 source to deliver a single dose (skin dose 900 rads) following a balloon overstretching injury to the central artery of the ear of NZW rabbits. The proliferative response was measured as the ratio of the neointima to media cross sectional area (I:M ratio). The irradiated arteries showed a significantly lower I:M ratio, when compared to the controls.

Mayberg et al (31) reported the effects of ionizing radiation on a standardized bilateral carotid balloon catheter arterial injury. The control arteries showed prominent NIH (neointimal hyperplasia) with marked reduction in luminal diameter. The test arteries were irradiated with doses ranging from 1 - 20 Gy. A prominent dose -response inhibition of intimal hyperplasia was observed between 1 - l0Gy with 50% inhibition occurring at 5 - 7.5 Gy. At doses equal to or greater than 10 Gy intimal hyperplasia was negligible. The effect of timing of the irradiation was also investigated. In keeping with the proliferation kinetics of the smooth muscle cells after injury, doses of 1 - 10 Gy were most effective if given at 24 hrs. post-injury, rather than later.

More recently, Williams et al confirmed these findings by showing that a dose of 5 - 15 Gy inhibited the appearance of neointimal hyperplasia in a dose- and time-dependent manner. Similarly, Marjianowski et al (32) have demonstrated the efficacy of 14 - 21 Gy LINAC-based external beam radiation therapy in inhibiting neointimal hyperplasia in a juvenile swine coronary balloon-overstretch model.

For reasons that are not entirely clear, the external beam studies have yielded less consistent results when compare to the endovascular approach. Some of this may be due to the use of inappropriate radiation techniques (e.g. orthovoltage energies), irradiation of large volumes of tissues (e.g. all, or most of the heart), flaws in the animal models used, and a failure to appreciate the interaction between the intervention/injury and the radiation modality (e.g. in the oversized tantalum stent injury model of Schwartz et aI, not only did the stents cause "severe" injury, but the use of orthovoltage radiation resulted in deposition of 3 - 4 times higher radiation doses in the immediate vicinity of the stent struts than what was prescribed).

Table 2 : Summary of Positive Studies Using External Irradiation

(Williams JP, Rubin, P, et al. Comparability of the external V s internal location of radiation in inhibiting neointimal hyperplasia. Cardiovasc Rad Med. 1999; 1 :55-63)

Weshler, Gotman, Okon et al	1988	Rat/aorta	Angioplasty	Orthovoltage	7-9Gy ↓ NIH 3 months postRx
Weshler. UrelskY,Okon. et al	1989	Dog/jugular vein	Transplanted graft	Orthovoltage	15Gy ↓ NIH
She fer. Eigler. Whiling, et al	1993	Rabbit/central artery of ear	Crush Injury	Tel etherapy. Sr-90	9Gy ↓ NIH
Shimotakahara. Mayberg et al	1994	Rat/carotid artery	Angioplasty	Teletherapy. Cs-137	7.5 Gy↔NIH.15& 22.5 Gy↓NIH 3 wks postRx
Abbas, Afshari. Satdius et al	1994	Rabbit/iliac artery	Angioplasty	6 MY. Linac	6G↔NIH.12Gy ↓ NIH 4 wks postRx
Mayberg, Luo, London. et al	1995	Rat/carotid artery	Angioplasty	Teletherapy. Cs-137	15&20Gy↓NIH3 months postRx
Sarac. Williruns, Riggs et al	1995	Rat/carotid artery	Angioplasty	HDR.lr-192	10 & 15 Gy↓NIH I month postRx
Hirai, Korogi. Harada. Takahashi	1996	Rabbit/femoral artery	Air drying	Orthovoltage	2-5 Gy↔NIH. 10 & 20 Gy↓NIH 4 wks. PostRx
Styles, Marijianowski, Robinson el al	1998	Pig/coronary artery	Overstretch (angioplasty)	6 MV, Linac	14 Gy↓NIH postRx (nonnalized for -ve remodeling)
Rubin, Williruns. Riggs et al	1998	Rat/carotid artery	Angioplasty	HDR.lr-192	10 Gy↓NIH I month postRx
Crocker et al	1999	Pig/coronary artery	Overstretch (angioplasty)	6 MV. Linac	21 Gy↓↓ NIH I month postRx

Table 3 : Summary of Negative Studies Using External Radiation

(Williams IP, Rubin, P, et al. Comparability of the external Vs internal location of radiation in inhibiting neointimal hyperplasia. Cardiovasc Rad Med. 1999;1:55-63)

Gellman. Healey. Chen et al	1991	Atherosclerotic rabbit/iliac artery	Angioplasty	Orthovoltage	3 & 9 Gy ↑ NIH I month postRx
Schwru1z. Koval. Edwards et al	1992	Pig/coronary artery	Angioplasty/Stent	Orthovoltage	4,4+4,8 Gy ↑ NIH at I month postRx
Hehelein. Kaiser. Kollum et al	1996	Rabbit/iliac artery	Stent	6 MV photons	8.8+8 Gy ↑ NIH 3 months postRx

Endovascular Studies

Hehrlein et al (33), from Germany, did a morphometric analysis of the rabbit coronary arteries after implantation of radioactive stents and compared that to the intimal response to implantation of regular stainless steel stents in a control group. At twelve weeks, the radioactive stents were seen to have completely eliminated the neointimal proliferation (which was marked in the control group).

Wiedermann et al from New York (34), reported the effects of pre-angioplasty irradiation on restenoses after balloon angioplasty in a porcine model. The test group received 20 Gy at the vessel wall via an intra-luminal iridium-192 source to the segment of the artery which was subsequently "injured" by dilatation. The test animals showed a significantly smaller intimal proliferation, with diffuse interstitial fibrosis in the media. No adverse radiation associated changes were noted in the adjacent adventitia, proximal or distal intima, epicardial fat or myocardium.

Waksman et al (35) from the Emory Clinic reported a similar experiment but also looked at the dose-response relationship and the effects of timing of XRT. They delivered 350 cGy, 700 cGy or 1400 cGy immediately post-dilatation or 48 hrs. after the dilatation injury. Though reduced neointima formation was seen even with 350 cGy, there was a prominent dose-response (the relationship is almost linear), with progressive reduction in the neointimal thickness with increasing doses upto 1400 cGy. Also, the response was more durable (6 months) with the higher doses. They found that the effects of radiation were more pronounced when delivered 48 hrs. after the injury, though immediate XRT was also effective. They also commented on the lack of any radiation associated changes/damage in the adjoining segments of the arteries or the cardiac wall.

Following these initial studies, numerous investigators have evaluated a variety of different isotopes and radiation delivery systems in animal models (most commonly the pig coronary model). Thus, gamma-emitters (Ir-l92 : manual loading, and high dose-rate remote afterloaders), beta-emitters (P-32, Y-90, Sr/Y-90), positron emitters (e.g. Cu-62), liquid isotopes (Rh-186, Re-188, Ho-166), gases (e.g. Xe-133), liposome encapsulated radioisotopes (Tc 99m) and radioactive stents "coated" with P-32 have all been studied with remarkably consistent results.

The biological plausibility is further underscored by evidence of a definite dose-response relationship in a number of these trials (Table 4)

Table 4: Evidence of a Dose-Response Relationship

(Parikh S, Nori D. Intravascular Brachytherapy -Clinical Trials In Human Peripheral Arteries, ASTRO Refresher Course, 1999)

External Beam Radiotherapy			
Shimotakahara, Mayberg et al	Rat/carotid	Teletherapy, Cs-137	7.5 Gy↔NIH, 15 & 22.5 Gy ↓ NIH 3 wks postRx
Hirai, Korogi, Ilarada, Takahashi	Rabbit/femoral	Orthovoltage	2-5 Gy↔H NIH, 10 & 20 Gy ↓NIH 4 wks. PostRx
Styles, Marijianowski, Robinson et al; Crocker et al	Pig/coronary	Linac-derived 6 MY photons	14 Gy ↓ NIH postRx (normalized for -ve remodeling);21Gy↓↓NIH
Rubin, Williams, Riggs et al	Rat/carotid	HDR,Ir-192	5 →15 Gy ↓NIH 1 month postRx
Endovascular Gamma Radiation Studies			
Waksman et al	Pig/coronaries	Ir-l92	↓ NIH with 3.5 - 14 Gy; sustained benefit at 6 months with 7 & 14 Gy
Weinberger et al	Pig coronaries	Ir-l92	↓ NIH with 15 -20 Gy; benefit continued at 6 months with 20 Gy
Mazur et al	Pig/coronaries	Ir-I92, HDR after loader	↓ NIH with 10, 15,25 Gy following angioplasty + stenting
Endovascular Beta Radiation Studies			
Waksman et al	Pig/coronaries	Sr/Y-90	↓ NIH with 7 - 56 Gy
Eigler et al	Pig/coronaries	Re-188 liquid filled balloon	↓NIH with increasing doses from 16 - 29 Gy in stented arteries
Weinberger et al	Pig/coronaries	Re-188 liquid filled balloon	↓ NIH with doses of 13.5 - 30 Gy at the balloon surface
Robinson et al	Pig/coronaries	Re-186 liquid filled balloon	Dose response with 5 - 30 Gy suppressing NIH and enhancing lumen size
Waksman et al	Pig/coronaries	Xe- I 33 gas filled balloon	7.5 - 30 Gy ↓ NIH after balloon injury

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9

Radiobiological Aspects Of Vascular Radiotherapy

Introduction

Following the discoveries by Roentgen and Curie in the late 1890s, both roentgen (X -) rays and gamma rays from radium were promptly used to treat a variety of diseases. Besides malignant neoplasms, a number of benign hyperproliferative conditions were very successfully treated with these new modalities. However, by the early 1900s it was clear that the effective therapeutic use of ionizing radiation required a delicate balancing act. The response of most of the normal tissues within a treatment field is usually similar (if not greater than) the response of the target tissue, i.e. the tumor. Under these circumstances, a favorable therapeutic ratio (tumor control, with acceptable normal tissue effects) can only be obtained via a complex interplay of physical and biological factors; these include the total dose, dose fractionation, treatment time, inherent radiosensitivity of the tissues, the proliferation status and various other biological and chemical radiation response modifiers. Understanding how ionizing radiations work and efforts to improve their effectiveness require a grasp of the biologic processes involved. This information can then be integrated with a clinical understanding of the proliferative process and normal tissue healing. This chapter emphasizes only those aspects of basic radiobiology as they relate to vascular radiotherapy; the interested reader is referred to several fine textbooks for a comprehensive discussion on the entire field of radiobiology (1, 2, 3).

Ionizing Radiations

Ionizing radiation can be either electromagnetic or particulate. The electromagnetic radiations consist of x-rays and gamma rays. *X-rays or gamma rays differ only in their origin, not in their physical or biological properties*. Therapeutic X-rays are most often produced by a device that accelerates electrons to high energy and then abruptly stops them in an appropriate target of tungsten or copper (Linear Accelerator). A part of the electron energy is dissipated as heat and the rest is converted to X-rays. Gamma rays are emitted from the nucleus of a radioactive isotope. When such an unstable nucleus decays by emitting some particle, the excess energy, above the stable energy level, is emitted as gamma rays. Particulate radiation includes electrons, protons, neutrons, alpha particles and mesons. Electrons (or beta particles) are commonly used in clinical practice and are negatively charged particles with a mass of about $1/2000^{th}$ that of a proton or neutron. They can be produced either in a linear accelerator, where they can be accelerated to a variety of different energies, or they can be the result of radioactive decay of unstable nuclei (beta decay). The basic characteristic of all ionizing radiation is energy dissipation by ionization (and excitation) of atoms and molecules of the absorbing material. Differences in the biological effects are mainly due to differences in spatial distribution and time of delivery of the absorbed radiation.

These ionizing radiations can be delivered in two ways. In *teletherapy*, the source is at some distance from the patient. This long distance is advantageous because the resultant dose distribution is relatively uniform across a given volume of tissue. In *brachytherapy,* the radioactive sources are placed directly within, or very close to, the target site. Because the intensity of radiation decreases in proportion to the square of the distance from the source, the dose gradient is steep and the normal tissues further away from the radioactive sources receive a much smaller dose.

Mechanisms of Radiation Injury

Ionizing radiation can effect tissue damage in two basic ways, *direct* and *indirect.* Direct injury occurs when an ionizing particle interacts with and is absorbed by the target biological macromolecule like DNA, RNA, proteins, enzymes, etc. About one-third of the total radiation induced injury is due to such a direct action, though numerous factors can change this. In the process of indirect injury, the ionizing radiation first interacts with cellular water to form highly reactive hydroxyl free radicals. These free radicals then interact with and damage the biological macromolecules. However, the cell has a very high concentration of organic matter which readily reacts with, and neutralizes these free radicals. The cellular water is thus a highly scavenged system, and the hydroxyl radicals are capable of creating damage only within a radius of about 10 mm (Table 1). The biological effectiveness of such radicals can be increased by the presence of oxygen or other electron-affinic molecules, such as nitroimidazoles. Conversely, sulfhydryl molecules are very effective scavengers and can reduce the efficacy of these radicals substantially.

Table I

Time Domains Of Radiation Action In Biological Systems

Physical Stage:	
10^{-18} to 10^{-17} sec	Fast particle traverses small atom or molecule
10^{-16}	Ionization $H_2 0 \rightarrow H_2 0^+ + e^-$
10^{-15}	Electronic Excitation $H_2 0$ Æ $H_2 0°$
10^{-13}	Molecular vibrations and dissociation
10^{-12}	Rotation, relaxation and solvation of the electron in water
Chemical Stage:	
10^{-10} to 10^{-7} sec	Reactions of solvated electrons and other free radicals with solutes in radiation tracks and spurs
10^{-7}	Homogenous distribution of free radicals.
10^{-3}	Free-radical reactions largely complete
Seconds, minutes & hours	Biochemical changes (enzyme reactions)
Cellular & Tissue Stages:	
Hours	Cell division is inhibited in microorganisms and mammalian cells : reproductive death.
Days	Damage to gastrointestinal tract (and CNS, at high doses)
Months	Haemopoietic death; acute damage to skin & other organs; late normal-tissue morbidity.
Years	Carcinogenecity & expression of genetic damage in offspring.

The *target theory* of radiation damage defines a target as a key molecule (essential for continued reproductive integrity of the cell) plus a sensitive area surrounding the key molecule. An interaction/ionization occurring within the target is called a *hit*. The assumption behind this theory is that ionization is a random phenomenon and any ionization occurring within the target is of far greater consequence to the cell than an ionizing event occurring elsewhere in the cell. Several lines of evidence point to DNA being the most likely target for ionizing radiation. Other damage, such as altered permeability of cellular/lysosomal/mitochondrial membranes, carbohydrate chain breakage, structural changes in proteins or lipids and alterations in enzyme functions may be supplementary mechanisms of cellular toxicity. Membrane injury, for example, is believed to be important in the interphase death of mature lymphocytes. Radiation can cause several types of DNA damage. These include:

1) Change/Loss of a base
2) Breakage of hydrogen bond between the two chains of the DNA molecule
3) Fracture (break) in the backbone of one chain (single strand break - SSB)
4) Fracture in the backbone of both chains (double strand break - DSB)
5) Fracture and subsequent cross-linking in the DNA molecule.
6) Local Multiply Damaged Sites (LMDS) - Fig. 9.1

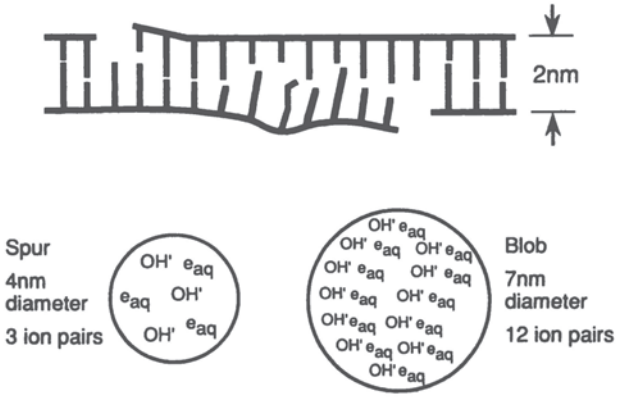

Figure 9.1 : Example of a Local Multiply Damaged Site. From: Hall EJ. Radiobiology for the Radiologist. 4th ed. Philadelphia, PA, J.B.Lippincott Co., 1994 - with permission.

All DNA damage does *not* lead to cell damage. Most of the damage can, and is probably, repaired with no adverse cellular consequences. Any unrepaired damage is essentially a mutation, and can have minor (cell alive, but "impaired"), or major (cell death) consequences. Amongst all the kinds of DNA damage, the double strand break, and local multiply damaged sites are least likely to be repaired and thus most likely to cause cell death.

It is important to remember that the interaction of radiation in the cells is purely a probability function, or a matter of chance. Radiation may or may not interact, and if interaction occurs, damage may or may not be produced. Also, the radiation interaction within the cell is nonselective. Thus, while there are critical targets present within the cell, the energy from ionizing radiation is deposited randomly throughout the cell; no areas of the cell are *chosen* by the radiation. Furthermore, the biologic changes resulting from radiation occur only after a latent period, which can vary from minutes to years. Finally, from a morphologic point of view, the

visible changes occurring as a result of the radiation interaction are not unique - they cannot be distinguished from damage produced by other kinds of trauma.

Cell Survival Considerations

When cells are exposed to ionizing radiation, they can undergo a number of possible fates:

1) Interphase death: This is also called *non-mitotic or non-division death*. Though this can occur in all kinds of cells, the dose required to destroy cell function in non-proliferating systems is extremely high - 20 to 100 Gy. One exception to this is the mature lymphocyte, which exhibits interphase death at very low doses (in the therapeutic range). Rapidly proliferating, undifferentiated cells can undergo interphase death at much lower doses. *There is no evidence that this constitutes a dominant or even a significant component of radiation-induced death in either endothelial cells or smooth muscle cells.*

2) Division Delay: In an asynchronously dividing cell population, irradiation disturbs the constant ratio of mitotic to non-mitotic cells (the mitotic index). Cells about to enter division are delayed in G2 phase for a variable amount of time, resulting in a fall in the mitotic index. If the radiation dose was low enough, the cells eventually recover and proceed through mitoses. This cellular response is called *mitotic or division delay.*

3) Reproductive death: Cell survival, or its converse, cell death, may mean different things to different persons; therefore, a precise definition is essential. From the narrow view of radiobiology, loss of reproductive integrity is equated with cell death. This is sometimes referred to as *reproductive death.* A cell may be physically present, apparently intact, may be able to make proteins or synthesize DNA, and may even be able to struggle through one or two mitoses; but, if it has lost the capacity to divide indefinitely and produce a large number of progeny, it is, by definition, dead; it has not survived. Thus, a dose of 100 Gy may be required to destroy cellular function in nonproliferating systems, but doses as low as 2 Gy are often enough for loss of proliferative capacity. A survivor that has retained its reproductive integrity and is able to produce a large clone or colony is said to be *clonogenic* (as a practical guide, if a cell is capable of undergoing six consecutive cell divisions, i.e. produce a colony with at least 50 cells, then it is assumed to be clonogenic). *Reproductive death is the usual mode of radiation-induced cell death and is the dominant mechanism of inhibition of smooth muscle cell proliferation by vascular brachytherapy.*

Many mathematical models have been proposed to describe the complex relationship between radiation doses and cell survival. The simplest relation is a constant exponential function. This concept is very important - because of this exponential relationship, a given dose of radiation results in a fixed *proportion* rather than a constant *number* of cells being killed. In such an exponential relationship, when we plot the surviving fraction on a logarithmic scale against the dose on a linear scale, we get a *cell survival curve* (Fig. 9.2). The most widely useful cell survival relationship is probably described by what is known as the linear-quadratic (L-Q) equation:

$$S = e^{-\alpha D - \beta D^2}$$

where S is the fraction of cell surviving a dose D, and α and β are constants. This relationship was first proposed by Chadwick and Leenhouts (4) on the basis of a molecular model of cellular inactivation. They assumed that double-strand breaks in DNA could arise either by a single particle track damaging both strands (the probability of this being directly proportional to the

dose, D), or by random ionizations producing lesions on opposite strands that just happen to be close enough to constitute a double-strand break (the probability of this being proportional to the square of the dose, D). While this strictly mechanistic interpretation is no longer accepted, the L-Q model is an adequate representation of data for any of the doses used in clinical radiotherapy, besides having the distinct advantage of only two adjustable parameters, α and β. Typical values for α vary from 0.1 - 1.0 Gy^{-1} and those for β range between 0.01 - 0.1 Gy^{-2} . Though the precise values of α and β are difficult to determine independently, the ratio α/β can be experimentally determined and has proven to be very useful in a variety of clinical and experimental radiobiological modeling. A large body of experimental work has confirmed that there are no characteristic differences in survival curves between normal tissues and tumors. Tumors generally resemble their normal tissue of origin in this respect.

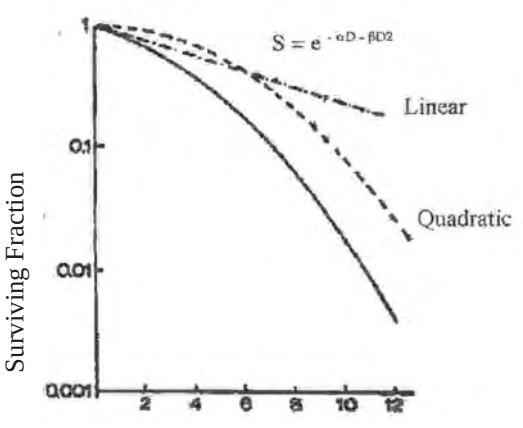

Figure 9.2 : Classic Cell Survival Curve

Repair of Radiation Damage

Radiation damage to cells can be divided into:

1) Lethal Damage, which is irreparable, irreversible, and by definition, kills the cell.
2) Potentially Lethal Damage (PLD) which is the component of radiation damage that can be modified by altering post-irradiation conditions. In general, conditions that prevent post-radiation cell division are the ones most favorable for repair of PLD.
3) Sublethal Damage (SLD) is the operational term used for the increase in cell survival seen when a given dose of radiation is split into two fractions separated by a time interval. This ability of the cell to repair some of the radiation damage, including a great proportion of the damage incurred at very low dose of radiation, probably accounts for the initial shoulder seen on the cell survival curves (if there was no repair, and damage was truly exponential, the curve would be a straight line at all radiation doses). When cell survival is assayed after exposure to two fractions of radiation separated by various time intervals, we observe the following: first, as the inter-fraction interval increases, more and more of the SLD gets repaired, resulting in progressively increasing cell survival (repair). Secondly, as the inter-fraction interval is further increased, there is a progression of cells through the cell cycle during the interval between the split doses. This serves to present the more sensitive phase of

the cell cycle to the next fraction resulting in an decline in cell survival (reassortment). If the inter-fraction interval is further increased beyond the length of the cell cycle, there is actual cellular proliferation between the two fractions, resulting in an increased surviving fraction (repopulation). The half-life of SLD repair is usually of the order of 30 - 90 minutes, and most of the repair is completed by 6 hours.

Cell Cycle Effects

Mammalian cells propagate and proliferate by mitoses. Cells that are not dividing are said to be in G_0 phase. When a cell enters the mitotic cycle, it traverses through a sequence of distinct phases: M (mitosis), G_1 ("gap" 1), S (DNA synthetic phase) and G_2 ("gap" 2). Elegant studies by Terasima, Tolmach and Sinclair in the 1960s (5) showed that cells vary in radiosensitivity as a function of their position in the cell cycle. Cells in G_0' i.e. cells that were not actively dividing, were the most radio-resistant. Amongst the cells in cycle, they found that the mitotic phase (M) is the most sensitive, and G_2 is almost as sensitive. G_1 is relatively sensitive in cells with a short

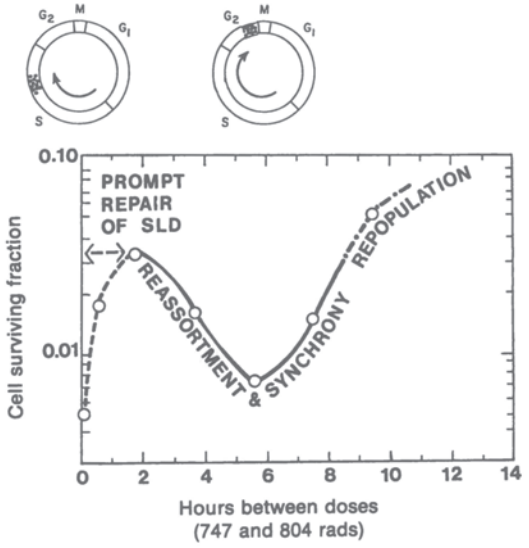

Figure 9.3 : Survival of Chinese hamster cells exposed to two fractions of radiation and incubated at 370 C for various intervals between the two doses. The survivors of the first dose are predominantly in a resistant phase of the cycle (late S phase). When the interval between the doses is about 6 hours, these resistant cells have moved to the G_2 - M phase, which is sensitive. From: Hall EJ. Radiobiology for the Radiologist. 4th ed. Philadelphia, PA, J. B. Lippincott Co., 1994- with permission.

G_1. Cells gradually increase in resistance as they proceed through the late G_1 and S phases, reaching a maximum resistance in late S phase (Fig. 9.3). The difference in radiosensitivity between a cell in mitoses and one in S phase is almost threefold. Though exceptions have been noted to everyone of these generalizations, these observations are generally applicable. Possible explanations for this variation in radiosensitivity include differential repair capacities, inability to arrest the cell cycle for repair or changes in the actual biophysical nature of DNA as it progresses through the cell cycle.

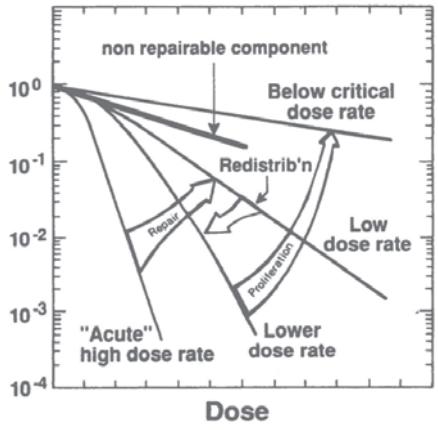

Figure 9.4 : Cell survival curves at various dose-rates. From: Hall EJ. Radiobiology for the Radiologist. 4th ed. Philadelphia, PA, J. B. Lippincott Co., 1994 - with permission.

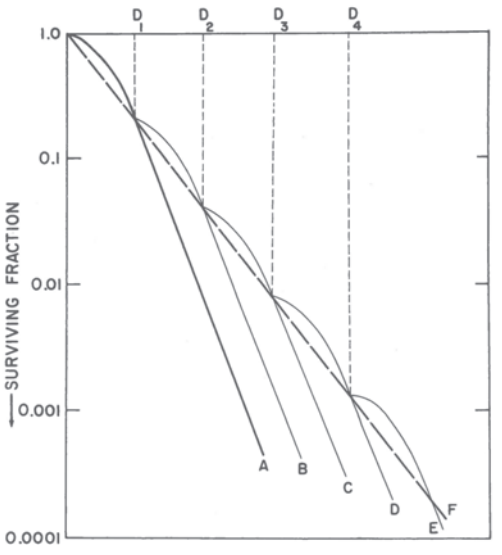

Figure 9.5: Idealized fractionation experiment. Curve A is the survival for single acute exposures of x-rays. Curve F is obtained if each dose is given as a series of small fractions of size D_1 with an interval sufficient for repair of sublethal damage to take place. Multiple small fractions approximate to a continuous exposure to a low dose rate. From: Hall EJ. Radiobiology for the Radiologist. 4th ed. Philadelphia, PA, J. B. Lippincott Co., 1994 - with permission.

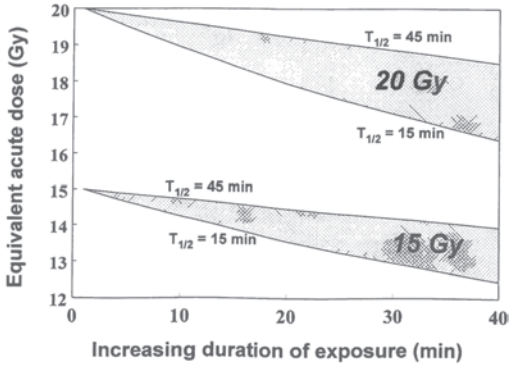

Figure 9.6: Interrelationship between treatment times, half times of repair and the biologically effective dose. From: Hall EJ, Miller R, Brenner D. Radiobiology of Intravascular Irradiation. In: Waksman R (ed) Vascular Brachytherapy, 2nd ed. Futura Publishing Company, Armonk, NY, 1999- with permission.

In the context of endovascular brachytherapy, it is important to remember that the medial smooth muscle cells are normally quiescent and non-cycling; the trauma of the angioplasty recruits these cells into proliferation. Given the marked variation in radiosensitivity as a function of the cell's position in the cell cycle, it is obvious that the timing of radiotherapy may be of some importance.

The Dose Rate Effect

Since both teletherapy, and more importantly, brachytherapy can be delivered at a variety of dose-rates, it is essential to appreciate the differences in biological consequences of the same dose of radiation delivered at different dose-rates (Fig. 9.4). The classic dose-rate effect results from the repair of SLD that occurs during a long radiation exposure. This is illustrated by an idealized experiment in which each dose (D2, D3, D4, and so on) is delivered in a number of equal fractions of size D, with an inter-fraction interval sufficient to allow for full SLD repair. In such a setting, the shoulder of the survival curve is repeated with each fraction, and if the number of fractions is large enough, one ends up with a shallow, straight survival curve with no shoulder (i.e. a higher level of cell survival) - Fig. 9.5.

This dose-rate effect is of clinical relevance as it is seen with the range of dose-rates employed in clinical radiotherapy, viz. about 1 Gy/min in external beam XRT or High Dose Rate Brachytherapy, down to about 0.3 to 0.6 Gy/hr. as employed in Low Dose Rate Brachytherapy.

The dose rate effect is of some importance in endovascular brachytherapy. The half time of repair (T½) of SMCs is probably of the order of about half an hour. Hence, whether a dose is given

in 3 or 5 minutes is of little importance; however, if the exposure time is prolonged to 30 minutes, the biological effectiveness of the dose will be reduced as sublethal damage repair can take place during the exposure. Thus, if the same nominal dose of 20 Gy is given over 30 minutes, its biological effect is only equivalent to 16.5 -18.5 Gy given in 1 minute (Fig. 9.6). This is an important factor to consider when results from different protocols are being compared.

Fractionation in Radiotherapy

Early in this century, as the practice of radiotherapy evolved, the virtues of dividing the radiation into small fractions were noticed. Now, more than 60 years later, we can account for the efficacy of fractionation based on relevant radiobiological experiments. The concept of fractionation is best understood in the context of the four Rs of radiobiology, which are believed to function during the inter-fraction intervals:

- Repair of sublethal damage
- Reassortment of cells within the cell cycle
- Repopulation of the tumor/normal tissue by multiplication of clonogenic cells
- Reoxygenation - Restoration of oxic conditions to hypoxic/anoxic areas of tumors as the radiotherapy progresses, thus increasing their radiosensitivity.

Thus, dividing the dose into a number of smaller fractions spares normal tissues, as it allows for repair of sublethal damage during the inter-fraction interval, and potentially for repopulation, if the total duration of therapy is long enough. On the other hand, the reoxygenation that occurs between fractions and the reassortment of cells into the radiosensitive phase of the cell cycle increase the extent of tumor damage.

Fractionation has important implications for normal tissue complications. Early responding tissues, such as the skin, mucosa and intestinal epithelium behave quite differently from the late responding tissues, such as the spinal cord, when the various elements of a fractionated radiotherapy regimen are altered. Based on the L-Q model, one can derive a unified quantity called the Biological Effective Dose (BED). This is a single quantity that incorporates the total dose, dose per fraction, number of fractions and the α/β ratio (it can even be "extended" to incorporate the total treatment time as a variable). The BED is expressed as :

$$\text{Biological Effective Dose} = nd\left(1 + \frac{d}{\alpha/\beta}\right)$$

where n = number of fractions, d = the fractional dose (such that nd = total dose), and α/β is the dose (with units of Gy) at which the linear and quadratic components of cell killing are equal. For early reacting or rapidly proliferating tissues, this value is generally 10-25 Gy, while for late reacting or slowly proliferating tissues (which usually determine the late side effects) this value ranges from 2 - 4 Gy. The importance of this concept lies in its ability to allow us to compare the biological effectiveness (in achieving a given level of cell kill) of two or more different dose fractionation schemes.

There is little data from the current clinical trials in endovascular radiotherapy to indicate the utility or, in fact, the feasibility of fractionated radiation therapy. However, basic radiobiological principles dictate that fraction size is the dominant factor in determining late effects - this would predict for a significant risk of late vascular effects with large single fractions,

as employed in endovascular brachytherapy. This underscores the need for a careful long-term follow up of all patients treated on current protocols. (Though fractionated endovascular brachytherapy has major logistical problems, the hemodialysis vascular accesses and even selected peripheral vascular sites can theoretically be treated with conventional fractionated external beam radiation using either electrons or photons.)

Volume Effect In Radiotherapy

The killing of individual cells is the basic effect of radiotherapy, and the tolerance of normal tissues to radiation depends upon the ability of the clonogenic cells to maintain a sufficient number of mature cells suitably structured to preserve organ function. Tissues may be thought of as composed of functional subunits (FSUs). The spatial arrangement of these FSUs is critical to tissue "survival". In tissues or organs where the FSUs are arranged in series, like the links in a chain, the integrity of every FSU is critical to organ function - elimination of even one FSU along the "chain" results in a probability of organ dysfunction. This directly leads us to the concept of the "volume effect" in clinical radiotherapy. Simply stated, this means "the total dose that can be tolerated depends upon the volume of tissue irradiated". In tissues with a serial FSU configuration (e.g. the spinal cord), increasing the volume of tissue irradiated leads to a much higher probability of tissue toxicity - the dose response curve correlating the radiation dose to the probability of tissue complication becomes progressively steeper with increasing volumes of tissue irradiated, and also moves towards lower doses. In contrast to this, the dose response is more graded in tissues with FSUs not arranged serially, since lower levels of injury can be healed by scattered clonogens that have survived throughout the irradiated volume (and even the adjoining unirradiated tissues).

The situation in the blood vessel is quite complex. On one hand, the endothelium can be considered as a "tissue" with FSUs that are not arranged in series; this model would not be expected to show a volume effect at lower levels of injury. However, when larger areas of the endothelium are denuded by the interventional procedure, and endovascular radiotherapy is added to this, the healing time may be quite prolonged (with an increased risk of interval

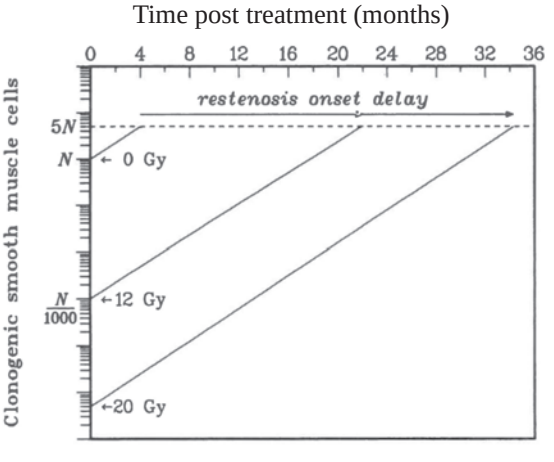

Figure 9.7: Estimation of the time course of restenosis onset delay. Assumptions = N clonogenic SMCs are present after the PTCA, without irradiation the restenotic process is complete within 4 months and the SMC population has to increase to 5 x N to cause restenosis. The slope of the line labeled "0 Gy" gives the baseline cellular proliferation rate. The downshift of the origins of lines labeled "12 Gy" and "20 Gy" on the y-axis represents the extent of depopulation of the SMCs achieved by the respective doses of radiotherapy. Since the basic proliferation rate is not affected, lines are drawn from these origin points parallel to the "0 Gy" line until they reach 5 x N, the restenosis level. The time at which the line intersects the restenosis level is the time, post-radiation, at which radiation-delayed restenosis would be predicted to occur, and this time minus 4 months is the radiation induced delay. From: Hall EJ, Miller R, Brenner D. Radiobiology of Intravascular Irradiation. In: Waksman R (ed) Vascular Brachytherapy, 2nd ed. Futura Publishing Company, Armonk, NY, 1999 - with permission.

thrombosis, i. e. vessel "failure"). On the other hand, if we consider the entire thickness of the vessel wall as one unit, the vessel can be visualized as having FSUs arranged in series, such that failure of any FSU (restenosis of a segment, or weakening of the vessel wall with pseudoaneurysm formation) would result in "failure" of the entire vessel. This model would be associated with a significant "volume effect". Data from ongoing trials, like the Long-WRIST study and others, will help clarify this further.

Radiobiology Of Vascular Radiotherapy

Brenner et al (6) have attempted to create a mathematical model of post-angioplasty restenosis, using specified assumptions, to predict the dose-response relationship and estimate the durability of the radiation response. Basic assumptions include an average interval from PTCA to restenosis to be about 4 - 6 months in most patients, and a 20% clonogenic SMC population in the media and intima. Assuming a cylindrical geometry of the artery, just one doubling of the SMCs would be enough to block the lumen. With 5% of the cells being clonogenic, 5 doublings would be required to cause this restenosis. Based on the known data about SMCs in vitro, a single dose of 12 Gy would result in a depopulation of about 10^{-3}, i.e. 1 in 1000 cells would retain clonogenic potential. These cells would have to undergo 12 divisions to block the artery.

Similarly, a dose of 20 Gy would cause sufficient cellular depopulation to require about 20 cell divisions to cause restenosis. The result would be a delay in the restenosis from 4 - 6 months without radiation to about 18 to 24 months post-XRT (Fig. 9.7). This would not necessarily be a minor achievement.

However, the SMCs are NOT tumor cells, and they are not likely to have the capability for indefinite reproduction. Normal somatic cells senesce after about 40 to 60 divisions in a young individual. With aging, due to progressive loss of telomeres (which act as a kind of biological clock), this capacity for continued cell division decreases, such that the same somatic cell may have a potential for less than 15 - 20 divisions in a 50 - 60 years old individual. On this background, it is easy to see how moderate doses of radiation (15 - 20 Gy) could potentially inhibit the restenotic process permanently. Also, there is some debate about whether one can indeed extrapolate a tumor like clonogenic model to this problem. When dealing with a cancer, it is essential to eradicate the last functional clonogenic cell to prevent what would otherwise be an inevitable recurrence. This is dictates use of the maximum tolerable dose in most cases. On the other hand, much lower doses give very good and durable results when radiation therapy is used for benign conditions (Table 2).

Table 2

Radiotherapy In Benign Disorders

Role Of XRT	Clinical Setting	Dose	Efficacy
Cosmesis	Keloids	10 - 15 Gy	75-95%
	Hemangiomas	8 - 16 Gy	> 75%CR
Function Preservation	Heterotopic Ossification	7 - 20 Gy	>96%
	Graves Ophthalmopathy	20 Gy	80%
Benign Tumors	Pituitary Adenomas	45 - 55 Gy	>90%
	Angiofibromas	30 - 40 Gy	>80%

Furthermore, the *timing* of XRT is believed to be of critical importance in radiation therapy for keloids and heterotopic bone formation. There is some preliminary evidence that this may also be the case in vascular radiotherapy, i.e. there may be a window of opportunity during which the radiation is most effective. In the case of heterotopic ossification and vascular restenosis, it is also seen that radiation given just prior to the intervention (when there are not expected to be any proliferating cells) is as effective as radiation delivered immediately after the intervention. This raises the intriguing possibility that the radiation may be inactivating a different target cell (rather than the SMC or osteoblast responsible for causing restenosis or heterotopic ossification). There is a lot of experimental evidence to suggest that the radiation related neointimal inhibition is not associated with any increase in apoptosis. Also, we now know that a complex cascade of signal transduction pathways and a myriad of growth factors are involved in the pathogenesis of neointimal hyperplasia. *Thus, it is entirely possible that appropriately timed radiation acts along the activation pathway and prevents the phenotypic switch of the SMC from a resting, contractile state to a proliferative, secretory cell* (7). Depending on the nature of the cells involved in this activation pathway, this could be achieved with far lower doses than those required to inactivate the very last proliferating SMC. Rubin et al (8) have presented some data to incriminate the macrophage-monocyte as the key cell in this process. These cells are known to be exquisitely radiosensitive; thus, modest doses of radiation could provide durable results in this setting. The recent observations that PTCA is associated with an upregulation of the NMMHC-B gene (nonmuscle myosin heavy chain-B), and that radiation can prevent this overexpression hints at some of the processes that may be involved at the molecular level in vascular radiotherapy.

Radiation Carcinogenesis

Cancer induction is the most important somatic effect of low dose ionizing radiation. Carcinogenesis may result from the activation of a protooncogene, the loss of a suppressor gene, or both. *Protooncogenes* are present in every cell and many have important functions in regulating cell growth or differentiation. Radiation may activate a normal protooncogene indigenous to the cell by either a point mutation, a chromosomal rearrangement or gene amplification, and these oncogenes act in a dominant fashion. About 50 such oncogenes have been identified so far, with the most common being the activated ras oncogene. *Suppressor genes,* on the other hand, are recessive. At present, there are six principal suppressor genes involved in a wide variety of human cancers. Mutations in the p53 gene is the most common expression of a suppressor gene. In general, two cooperating oncogenes are required for expression of the malignant phenotype. Oncogene products that act in the nucleus (causing immortality) cooperate best with those acting in the cytoplasm (causing loss of contact inhibition), e.g. the interaction between the *ras* and the *myc* oncogenes in transforming rat fibroblasts, etc.

The human experience of radiation induced carcinogenesis includes the survivors of the A-bomb, patients exposed to medical irradiation, and early workers exposed occupationally. The shortest latent period is for leukemias (5 - 7 years), while solid tumors can manifest even after 45 years. The most recent reassessment of radiation-induced cancer risks was by the BEIR V committee. They assumed excess cancer mortality to depend on dose, $(\text{dose})^2$, age at exposure, time since exposure and sex (for some cancers). Based on this and other data, the ICRP suggests a risk estimate of excess cancer mortality in a working population of 8×10^{-4} per sievert for high doses and high dose-rates, and 4×10^{-4} per sievert for low doses and low dose-rates. For the

general population, due to the increased susceptibility of the young, the risks are about 20% higher. The ICRP estimates that, on average, 13 - 15 years of life are lost each year for each radiation induced cancer, and that death will occur at age 68 - 70 years.

Studies of hundreds of thousands of radiotherapy patients show a small, but definite, incidence of second malignancies in long-term follow-up. Such tumors may occur in heavily irradiated tissues or in remote organs. An important point to note is that radiation carcinogenesis is a stochastic effect; that is, the probability of the effect increases with dose. There is no dose threshold, and the severity of the effect is not dose related. The issue is further confounded because a large number of these patients are more prone to develop a second cancer than the general population regardless of the mode of therapy; this could either be due to a genetic predisposition which induced the first cancer or due to the effects of exogenous carcinogens, like smoking, which can produce a field change or affect multiple different organ systems.

While most patients who develop second, in-field cancers following therapeutic radiotherapy would have received much higher doses than those proposed for vascular radiotherapy, radiation is a known carcinogen, and there is almost certainly a small - but real - risk of radiation-induced malignancy in any setting in which ionizing radiation is employed. On this background, it is interesting to review the use of radiation therapy in preventing keloid formation (9). These are usually young patients who have a much larger volume of tissue irradiated (when compared to endovascular brachytherapy), and are usually treated with doses similar to those employed in the vascular setting - a twenty year follow-up report from the Mallinckrodt Institute did not reveal a single instance of in-field malignancy in these patients !

Note: Numerous other radiobiologic issues of great relevance to radiation oncology, such as Hypoxia & the Oxygen Effect, RBE, LET, Heavy/Charged particle Radiations, etc. are thought to be beyond the scope of this discussion. Hypoxia may be important, especially when using centering catheters, which could occlude blood flow through the vasa vasorum and make the vessel wall locally ischemic (and thus, relatively radioresistant) - Fig 9.8; also, radiosensitizers, like bromodeoxyuridine, etc. could potentially be used to improve the therapeutic ratio. However, the actual relevance of these issues to vascular radiotherapy is not obvious at this point, and the interested reader is referred to any of the several standard textbooks on this matter for further information.

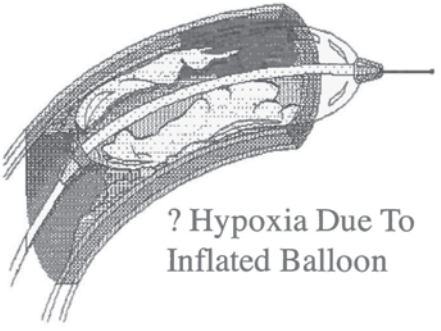

Figure 9.8 : Centering Balloons And The Potential For Vessel Wall Hypoxia. Copyright LifeART Collections, Lippincott, Williams and Wilkins.

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10

Radiation Physics For Vascular Brachytherapy

This chapter is aimed at equipping the interested reader with the background information necessary to critically evaluate the use of radiation to control restenosis. It is not intended to be a comprehensive treatise on radiation physics - many fine textbooks and reviews serve that purpose (1 - 5). Only basic physics terminology will be introduced and linked to the specific application of vascular radiotherapy.

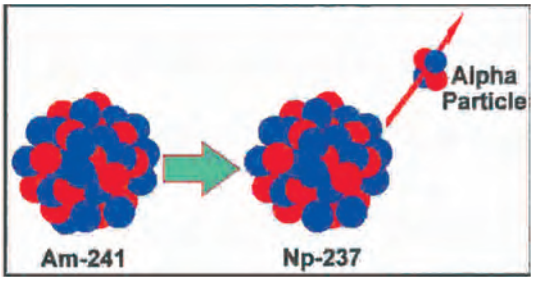


Figure 10.1: An example of radioactive decay with the "ejection" of an alpha particle

Radioactivity (1)

Within the confines of the atomic nucleus, protons and neutrons are in constant motion. As a result, collisions occur & energy is transferred back and forth between these particles. In stable nuclei, no particle ever achieves enough energy to overcome the nuclear binding force and escape from the nucleus. In radioactive nuclei, however, it is possible - through a series of chance encounters - for a particle to gain enough energy to escape from the nucleus (Fig. 10.1). The ejection of a nuclear particle is pure chance; there is no way to predict which particular nucleus will disintegrate, or when. But, if there are enough nuclei, a certain fixed percentage will disintegrate in a given time with the ejection of α or β particles or γ rays. Such radioactive nuclei can be either natural (all elements with an atomic number > 82 have at least one unstable, radioactive isotope), or artificially created in a nuclear reactors by bombardment of stable nuclei with neutrons.

Activity

The activity of a radioactive isotope is defined as "the number of disintegrations occurring per unit time". The transformation constant, A relates the number of atoms present to the activity of the source, such that

$$\text{Activity, } A = N_0 \lambda e^{-\lambda t}$$

where N_0 is the initial number of atoms present, A is the transformation constant & t is the elapsed time. Since this disintegration behavior is exponential, we get the following relationship,

$$\text{Half-life, } t_{1/2} = 0.693/\lambda,$$

where the half-life is the time that must elapse for the activity of a source to decay to half its initial value.

The S.I. unit for activity is Becquerel (Bq), where 1 Bq = 1 disintegration per second. The older unit for activity was Curie (Ci), and 1 Curie was defined as the number of disintegrations per second from a gram of radium (millicuries are still more commonly used as units than bequerels).

$$1\text{Curie} = 3.7 \times 10^{10} \text{ Bequerels}$$

Radioactive Decay

There are several ways in which a radioactive nucleus can decay:

β *decay* : Here, a neutron within the nucleus gets converted to a proton, and an electron & antineutrino are emitted (β^- decay) or a proton within the nucleus gets converted to a neutron with the emission of a positron and a neutrino (β^+ decay). A positron is a positively charged particle with the same mass & spin as the negatively charged electron, and the neutrino & antineutrino are subatomic uncharged particles with a mass less than 1/8000 th of an electron. In β decay, the emitted particles possess a spectrum of kinetic energies; the maximum kinetic energy of these particles is rarely greater than 3 MeV of clinical importance is the concept of mean energy, which is lower than the most energetic β particles emitted. A common example of β^- is the decay of radioactive phosphorous, ^{32}P to sulfur:

$15^P \rightarrow 16^S + \beta^- + v$, where v is the neutrino, and β^- is the electron or" β particle"

The total energy released is 1.71 MeV. This is shared between the electron and the neutrino. The electrons emitted have a spectrum of energy with the maximum being 1.71 MeV; but the mean energy of the electrons is 0.695 MeV. Another common isotope which is relevant to vascular brachytherapy is Yttrium-90. This is a radioactive isotope obtained by decay of Strontium-90. It decays to Zirconium, with a maximum beta energy of 2.27 MeV. Similarly, Ruthenium-106 exists in radioactive equilibrium with Rhodium-106, and emits beta rays with a maximum energy of 3.5 MeV

In other beta-minus decay processes, there is a concomitant emission of one or more γ rays which form the therapeutically useful component of the emissions while the electrons are absorbed in the source "capsule". Examples of this include the decay of radioactive Iridium-192, Cobalt -60 and Cesium-137.

α *decay*: This occurs mainly in heavy nuclei. A helium nucleus (or alpha particle) - consisting of 2 neutrons and 2 protons - is ejected with or without an associated γ ray. A common example in clinical use is the decay of Radium to Radon.

γ *decay*: Here a nucleus undergoes a transition from a higher energy level to a lower, more stable energy level, and the excess energy is got rid off as γ rays.

Other related decay processes include electron capture, internal conversion, & emission of Auger electrons.

Interaction of X-Rays With Matter

Absorption of Energy

When a photon beam passes into an absorbing medium such as body tissues, some of the energy carried by the beam is transferred to the medium where it may produce biological damage. *The energy deposited per unit mass of the absorbing medium is known as the absorbed dose.* This has S.I. units of Gray, such that

1 Gray (Gy) = 1 Joule/kg., and

1 Gray = 100 centigray (cGy) {1 cGy is equivalent to 1 rad}

Beam Attenuation

Photons can interact with matter in several different ways (Photoelectric absorption, Raleigh scattering, Compton scattering, Pair production, & Photodisintegration). In any given situation, the beam energy and the characteristics of the absorbing material (mainly its atomic number) determine which of these mechanisms predominates. In general, above photon energies of 100 kV, Compton scattering predominates; the probability of this type of interaction (and dose deposition) is largely independent of the nature of the tissue. For lower energy photons, photoelectric absorption predominates; the probability of this interaction (and dose deposition) varies greatly with the nature of the interacting tissue - dose deposition is directly proportional to the Z^3 of the tissue (Z = atomic number). *From the point of vascular brachytherapy, higher energy gamma emitters like Ir-I92 are minimally affected by tissue inhomogeneities like a calcific plaque or presence of stents; on the other hand, a low energy gamma source like Iodine-125 or Palladium-103 is likely to deposit almost 4 times as much energy within a calcific plaque or a stent as compared to normal tissue. This results in a shadow (or area of underdosing) being cast directly behind the plaque or stent.*

The probability that a photon will interact as it traverses through a given thickness of material is the product of the individual interaction probabilities for each of the above five processes. Mathematically, we have

$$N = N_0 e^{-\mu t}$$

where N_0 is the number of incident photons impinging on an absorber of thickness t, N is the number of photons traversing the absorber without interaction and μ is the linear attenuation coefficient (i.e. it represents the fraction of photons that interact per unit thickness of the absorber).

A thickness of material that reduces the number of photons transmitted to one half the incident number is called the *half-value layer (HVL) or half-value thickness.*

$$HVL = 0.693/\mu$$

Dosimetry

Percentage Depth Dose

This gives us an idea of the absorbed dose at different depths along the central axis of a beam that is incident on the surface of a medium. "Percentage Depth Dose (PDD)" is defined as the ratio of the absorbed dose at any depth "d" to the absorbed dose at a fixed reference point "d_0" along the central axis of the beam, when expressed as a percentage".

$$PDD = (\text{Dose at depth } d / \text{Dose at depth } d_0) \times 100$$

Isodose Curve:

An isodose curve represents points of equal dose. A set of these curves, usually in increments of 10%, normalized to the dose at the reference depth, can be plotted to give a visual representation of the dose distribution in one plane. Beam parameters such as source size, field size, the distance of the source from the skin, use of filters, etc. play a crucial role in the shape of the isodose curves.

Inverse Square Law

Though clinical sources have finite dimensions, when one is concerned with doses at distances which are relatively large in comparison to the source size, the source can be assumed to be a point. The exposure rate (or "dose rate in free space") from such a source varies inversely as the square of the distance from the source (Fig. 10.2) . This rather obvious relationship is of fundamental importance in radiotherapy , and is especially important in brachytherapy , as we shall see later .

There are numerous other parameters of great importance for clinical radiation dosimetry; however , a detailed discussion of these is beyond the scope of this manual and interested readers are referred to any of the standard texts on this matter .

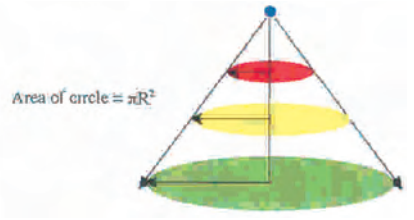


Figure 10.2: The Inverse Square Law - the radiation from a point source diverges out equally in all directions. As one proceeds away from the source, the same number of "rays" are intersected by a larger and larger circle, resulting in a reduction in the intensity of the radiation (number of "rays" per unit area). Using the principle of equivalent triangles, it is obvious why this intensity decreases in proportion to the square of the distance from the source.

Electron Beam Therapy

Electron beams for clinical applications are obtained from High Energy Linear Accelerators and Microtrons Except for differences in particle energies , these electrons are identical to the β-particles emitted from beta emitting isotopes .

Electron Interactions

As the electrons (β^- particles) travel through a medium, they interact with atoms by a variety of processes. These interactions can be elastic, wherein there is no loss of kinetic energy (though it may be redistributed amongst the interacting particles, e.g. elastic collisions with nuclei or atomic electrons). Or they can be inelastic, wherein there is actual loss of the kinetic energy of the electron - this may either be due to interaction with orbital electrons, causing excitation/ionization, or due to interaction with the nuclei of the absorbing material and production of *Bremsstrahlung X-rays.*

Characteristics of Clinical Electron Beams

1) Depth doses along the central axis:
   - The skin dose increases with increasing electron energy.
   - The beam gets attenuated by about 2 Me V/cm. of tissue.
   - The 80% isodose is at a depth approximately equal to one-third the nominal energy of the beam (e.g. at 2 cm. for a 6 MeV beam).
   - The 90% isodose is at a depth approximately equal to one-fourth the nominal energy of the beam (e.g. at 1.5 cm for a 6 MeV beam).
2) As the beam penetrates the medium, it "expands" rapidly below the surface due to scattering. However, there is considerable variation in the spread of individual isodoses. Thus, for low energy electron beams, all isodoses bow outwards, whereas for high energy beams, only the lower isodoses bulge out, while the higher isodoses actually show a lateral constriction. This factor has to be taken into account while designing fields for treatment with electron beams.

3) Unlike megavoltage X-ray beams, electron beams exhibit a very rapid fall-off, especially at energies below 15 MeV. This is highly significant as there is basically no dose other than that from X-ray contamination (from Bremmsstrahlung), to the tissue beyond the *practical range* (As a rule of thumb, the practical range = half the nominal energy of the electron beam, e.g. 3 cm. for a 6 MeV electron beam). This characteristic drop-off in dose beyond a particular depth is the major advantage of electron beams as superficial structures can be treated without any significant dose to the underlying, deeper tissues

Brachytherapy Physics

Brachytherapy is a mode of radiation therapy in which radiation is delivered from a short distance by surface application or by interstitial/intracavitary insertion of radioactive sources. The major advantages associated with this approach include:

1) Because of the inverse square law ("dose is inversely proportional to the square of the distance from the source"), the radiation dose is limited to the area of concern, with sparing of normal tissues, some of which can often be dose-limiting structures. This makes it possible to deliver higher doses and improve the therapeutic ratio.
2) The dose distribution can often be made to conform to any desired irregular shape, which again limits the dose to the normal tissues.
3) The overall treatment time is reduced - this overcomes the problem of repopulation during the course of radiotherapy.
4) There are also some important radiobiologic advantages, especially with low dose-rate brachytherapy.
5) In most instances, brachytherapy is quite cost-effective.

There are some disadvantages/limitations with the use of brachytherapy:

1) Special skills are needed for successful implementation.
2) It is impractical for large volumes.
3) May need a surgical/invasive procedure.
4) Small uncertainties can result in large dose variations - this is especially relevant when one uses of beta-emitters for endovascular radiotherapy, due to the very rapid dose fall-off.
5) Radiation protection issues come into play.

Brachytherapy procedures may be classified in several different ways:

1) Temporary
   Permanent
2) Sealed sources (most instances)
   Unsealed sources (e.g. colloidal gold solution, colloidal radioactive phosphorous)
3) Preloaded - here the radioactive sources are directly implanted in the target volume. Manually afterloaded - here one just implants hollow tubes in the target volume, and these are manually "loaded" with the sources at a later time (e.g. the Cordis Checkmate™ System).

Remotely afterloaded - again only hollow tubes are implanted in the target volume, and these are later loaded by computer driven units via remote control (e.g. the Guidant Galileo™ System).

4 *Low dose-rate* = 0.4 to 2.0 Gy/hr.

Intermediate dose-rate = 2.0 to 12.0 Gy/hr
High dose-rate = > 12 Gy/hr (i.e. > 0.2 Gy/min., usually >1 - 2 Gy/min.)

Basic Brachytherapy Terms

- Physical Length: This refers to the actual total length of the source, including the capsule and any spacers that may be present.
- Active Length: This is the distance between the ends of the radioactive material (this is usually surrounded by a capsule).
- Activity or Strength of a source: This is usually expressed in terms of millicuries (mCi) or mg. of radium.
- Linear Activity: Activity/Active length.
- Specific Activity: Activity per unit mass of the isotope.
- Exposure Rate Constant: This is a measure of the inherent radioactive intensity of a radioisotope (the activity just tells the number of disintegrations that occur per unit time). It is a measure of the exposure rate at a particular distance from a source of given activity.
- Air Kerma Strength: Kerma stands for “Kinetic Energy Released in Medium”, and is measured in J/Kg or Grays (Gy). The Air Kerma Strength is being used increasingly for the specification of brachytherapy sources. It is defined as "the product of air Kerma rate in "free space" and the square of the distance of the calibration point from the source center along the perpendicular bisector", i.e.

$$S_K = K_l \times 1^2$$

where S_K is the air Kerma strength, and K_l is the air Kerma rate at a specified distance 1 (usually 1 meter).

Common Brachytherapy Sources:

Suitability of a given isotope for brachytherapy is determined largely by its half-life, and by the type, energy and abundance of its emission. For vascular brachytherapy sources, the size constraint means that we need isotopes with a high specific activity, while the requirement for short treatment times necessitate a high exposure rate constant.

The Ideal Radioactive Source

The ideal brachytherapy source is a single, infinitely small, encapsulated, monoenergetic point source that would interact with the tissue in the same manner as with air. The activity of the source would be precisely known. The radiation emitting from the source would be governed by the inverse square law and would be isotropic (i.e. of equal magnitude in all directions around the source). *For endovascular brachytherapy, size is very critical but the source should also have a high output, i.e. a high specific activity (to allow the treatment to be completed within a short time), and emit low energy radiations to limit the radiation to the normal tissues.*

Penetrability of Brachytherapy Sources

The penetrability of brachytherapy sources is commonly expressed by their half value layer (HVL) or tenth value layer (TVL) in lead or tissue. While this is applicable to gamma-emitters, for beta-emitters, the range in tissue (in cm.) is very short, about half of the maximum beta-ray energy in MeV. Thus, for ^{32}P with a 1.71 MeV beta-ray, the range in tissue is only about 0.8 cm. (Note: This is the distance at which *any* significant radiation is detected; the clinically significant dose is limited to the first 2 - 3 mm). Thus, beta-emitters are adequately shielded by a few mm. of tissue and the concept of HVLs is not commonly applied to them. This short range often has a therapeutic advantage, but it also means that they cannot be effectively encapsulated (the capsule material would shield most of the radiation!).

The Physics of Vascular Brachytherapy

The dosimetric requirements for intraluminal treatment via temporary insertion of radioactive sources can be summarized as follows (3):

- Single, dose of 10 - 30 Gy to a 2 to 4 cm length of vessel (may be much longer in the periphery), which has an inner diameter of approximately 2 - 5 mm, and a wall thickness of 0.5 to 3 mm;
- High dose volume confined to the region of the angioplasty injury, with minimum dose to the surrounding normal tissues including the myocardium;
- Dose rates greater than 2 Gy/min to keep dwell times (i.e. treatment times) < 15 minutes;

The radioactive source must have dimensions, stiffness and flexibility compatible with use with angioplasty catheters. Thus source diameter must be 0.5 - 1.0 mm, and yet be stiff enough to negotiate greater than 100 cm arterial length, be flexible enough to negotiate the multiple bends encountered in the coronary arterial tree, and yet have uncompromising source integrity.

The ideal source would be a low energy gamma-emitter (100 kev) with an activity greater than 1 Ci. Unfortunately, this is yet not practical. Although several low energy gamma-emitting isotopes have been considered (I-125, Pd-103, etc), none are currently available at high enough specific activity to be useful. The reason for this is that gamma and x-rays deposit relatively little dose in tissue per radioactive decay, and large amounts of radioactive material (1 Curie or more) are required to yield adequate dose-rates. Limitations on source size makes fabricating these sources with sufficient activity a challenging proposition. I-125 and Pd-103 are also associated significant problems of source anisotropy (a situation in which there is a marked difference in the dose distribution along the long axis of the source when compared to that along the short axis of the source).

Unlike gamma/x-rays, beta particles have a very short and finite range within tissues, proportional to their energy. A pure beta minus emitter (i.e. one that does not emit any gamma rays) with a transition energy of > 3 MeV would provide a dose distribution as good as iridium-l92 over the distances required in intravascular brachytherapy, with no radiation safety problems or concerns of normal tissue toxicities. "Betas" also deposit 20 - 50 times higher dose per emission than do "gammas", so required beta activities are at least an order of magnitude less than for gamma sources. This makes source fabrication in a small enough size a relatively easy

proposition. Unfortunately, most beta-emitters with suitably high energy have a very short half-life or also emit significant amounts of gamma radiation. The only way to obtain a beta-emitter with both higher energy and a longer half-life is to use a parent-daughter combination of isotopes in radioactive equilibrium. This is a situation where a parent isotope (such as Sr-90, Ru-106, or W-166) decays with a long half-life but with low beta energy into a second, or daughter isotope (Y-90, Rh-106, or Re-188 respectively) with a short half-life, but higher and therapeutically more useful beta energy. Thus the net result is an isotope-pair which "appears' to decay with the half-life of the parent, while emitting a relatively high energy beta from decay of the daughter. Of the 3 such pairs identified, Sr/Y-90 has a marginal energy (average 970 keV; max 2270 keV), while Ru-106/Rh-106 and W - 188 / Re - 188 have significant gamma contamination. Also, the energy of the W-188/Re-188 pair is marginal (average 78 keV; max 2130 keV), though Ru-106/Rh-106 has a near ideal energy profile (average 1180 keV; max 3540 keV).

Traditionally, in tumor brachytherapy, the dose to the target is prescribed at a distance of 1 cm from the center of the source. At this standard distance, the dosimetry for brachytherapy sources is well established. Unfortunately, in vascular brachytherapy, the intended target volume is not only not clearly identified, but is likely to be within 1 - 3 mm from the source center. At these short distances, the dosimetry is somewhat uncertain due to very steep dose gradients. Another source of uncertainty is the potentially significant contributions from low energy secondary radiations, such as fluorescent X-rays, beta- or alpha-particles, secondary electrons, etc., all of which are normally absorbed within the first few millimeters of irradiation, either within the source encapsulation on in the immediate surrounding tissues. There may also be important self-shielding effects from the design of the sources, indwelling catheters, guide wires, stents and plaque calcifications which add to the complexity of the dosimetry. Source anisotropy may be another complicating factor. Non-centering of sources and the presence of an eccentric vascular lumen (even in the face of a perfectly centered source) can greatly aggravate the dose inhomogeneity. Radioactive stents add an entirely new dimension to this problem of complex dosimetry. In fact, as things stand today, there is no standard dosimetry system for these very low activity stents, and the prescription is based solely on the stent activity.

The AAPM recognized the complexity of the situation and has designated a task group, AAPM TG-60, to consider these issues. Apart from medical physicists, the task force also has representatives from interventional cardiologists and radiation oncologists to tackle this truly multidisciplinary problem. The task group's report was approved by the AAPM Science Council on November 30, 1997(6). The 16 major recommendations of the report include:

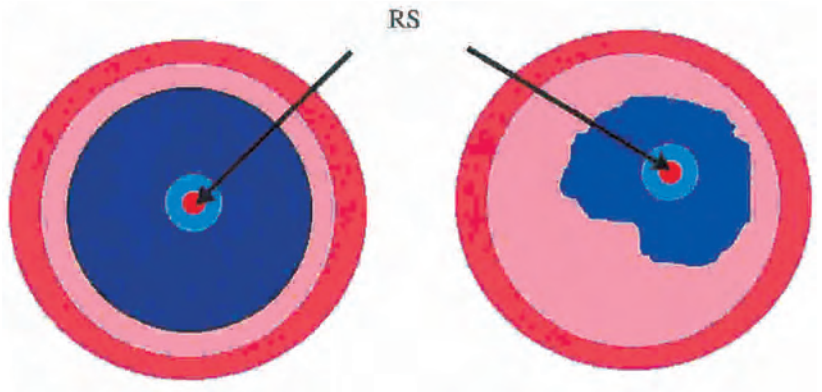
1. Source strength of a catheter-based system must be expressed in terms of air-kerma rate in air for gamma sources (air kerma strength) and dose rate in water at a reference distance of 2 mm for beta emitters.
2. Dose distributions around a catheter-based brachytherapy source should be determined using the AAPM TG 43 protocol for photons and a modified version of the same protocol for beta sources.
3. Source strength of a catheter-based system should be traceable to a national standard at NIST or at an ADCL.
4. The radial dose function, geometry function and anisotropy function should be determined for each specific source design of a commercial catheter-based system.

5. Clinical prescription for a catheter-based system should be expressed in terms of dose delivered at a reference depth in water.
6. For a catheter-based system, depth of dose prescription for intracoronary applications should be at a radial distance of 2 mm from the center of the source and for peripheral vessels 2 mm larger than the average lumen radius. Average lumen radius should also be reported.
7. For optimal assessment of each clinical case, average, minimum, and maximum doses delivered should be estimated in at least three planes perpendicular to the catheter and along its length.
8. The output of all commercial intravascular brachytherapy catheter-based systems should be specified in terms of the dose rate in water at a radial distance of 2 mm from the center of the catheter.
9. The penetrating ability of all commercial intravascular brachytherapy catheter-based systems should be specified in terms of radial dose function normalized at a distance of 2 mm and at radial distances from 0.5 to 10 mm (or R_{90}, 90% of the electron range for beta emitters), at 0.5 mm intervals, with a reference depth of 2 mm.
10. Uniformity of dose delivered by catheter-based systems at points both along the source axis, at r = 2 mm, and around the circumference of a 2 mm radius circle centered on the source axis in a plane perpendicular to it should be better than +/- 10% (range of values from maximum to minimum in the centered two-thirds of the treated length along the catheter axis.
11. For each catheter-based system, an atlas of 3-dimensional dose distributions should be generated to estimate dose variation in the target.
12. Clinical prescription of radioactive stents should be in terms of a) stent diameter, nominal & deployed, b) stent length, c) stent type, brand, model, d) radioisotope, e) activity.
13. The measured activity of a radioactive stent should be traceable to a national standard at NIST.
14. Activity for each stent to be used should be determined using an appropriate transfer technique.
15. For radioactive stents, relative doses at 0.5 mm radial distance from the surface of the stent in the midplane and over time periods of 28 days should be reported.
16. The quality assurance program presented in this AAPM TG report should be followed under the direction of a qualified medical physicist.

The Problem Of Source Centering (7)

Due to the steep dose gradients associated with brachytherapy sources, a non-centered source has the potential for resulting in significant dose-inhomogeneity in different sectors of the vessel wall. Based on this theoretical consideration, proponents of "centering" claim that a source that is well-centered within the arterial lumen, could reduce the dose-inhomogeneity; this could minimize the risks of under-dosing due to "cold spots" and reduce the potential late toxicity from "hot spots" that could result from the source coming near or in contact with the vessel wall.

The problem with this concept is that the atherosclerotic plaque is usually eccentric, and the post-angioplasty lumen is also eccentric. Thus, even if the source is perfectly centered within the lumen, it would not be centered with respect to the target volume (Fig. 10.3).



Idealized Geometry With A Central Lumen - Centering Balloon Can Truly Center The Radiation Source (RS): A = B

Real-Life Geometry With A Markedly Eccentric Lumen - A Centering Balloon Can Center The Source (RS) Within The Lumen, But Not In Relation To The External Elastic Lamina: A < B

Figure 10.3: Eccentric Plaque Resulting In Non-centering With Reference To The Target, Despite Centering Within The Lumen

Active centering devices like balloons add an additional dimension of complexity to an already complicated situation; furthermore, they occlude antegrade blood flow in the coronary artery and can cause ischemic symptoms during the radiation delivery (the Guidant™ system attempts to circumvent this problem by using a spiral balloon, which allows perfusion around the balloon, while maintaining a centered position). Also, a centering balloon can potentially make the arterial wall ischemic by occlusion of the vasa vasorum, and thus reduce the efficacy of the radiation (Fig. 10.4).

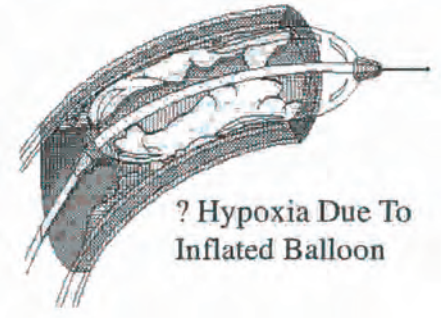


Figure 10.4: Centering balloon showing the potential for compressing the vasa vasorum and causing vessel wall hypoxia, resulting in radio-resistance of the target cells. Copyright LifeART Collections, Lippincott, Williams and Wilkins.

The arterial lumen in the coronaries is small enough, and the catheters of some of the delivery systems are large enough that an element of self-centering is automatically achieved. The pulsatile coronary blood flow, and the cardiac contractions have an additional effect of "blurring out" the eccentric positioning of the catheter. It should be noted that the clinically positive studies to date (Condado et al; SCRIPPS; WRIST; GAMMA-I; START) all used non-centering systems.

It has been argued that centering may be more important in the setting of the higher dose-gradients associated with the beta-emitters. However, some of the largest clinical trials using a beta source, the Novoste™ studies - BetaCath, START - are being done with an non-centered system; on the other hand, the Guidant™ and Boston Scientific/Schneider™ systems do employ a centering system with beta-isotopes.

Centering is absolutely critical when intravascular brachytherapy is used in larger peripheral vessels like the femoro-popliteal arteries, AV dialysis shunts and TIPS (Fig. 10.5).

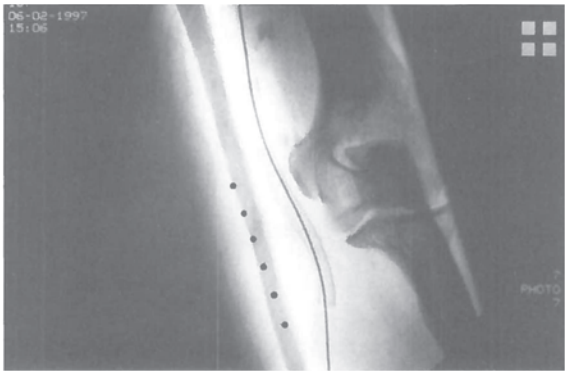


Figure 10.5 : Dialysis Access Stenosis, showing the potential for dose inhomogeneity without a centering device.

Isotope Selection

1. *Gamma emitters (e.g., Ir-192):*

Advantages-

1. Higher average energy allows delivery of adequate dose to the adventitia, an important consideration given the uncertainty regarding the actual "target layer".
2. Shallower dose gradient results in a relatively lower dose to the intima for any level of prescribed dose into the vessel wall - an important consideration for late side-effects.
3. The higher energy may be somewhat more "forgiving" of minor positioning errors.
4. Less problems of shielding/underdosing as a result of stents, plaque, and calcium.
5. Generally, these isotopes have reasonably long half lives.
6. The relatively long treatment times mean
   - very insignificant transit dose to normal tissues, a somewhat higher margin of safety if source deployment is delayed by a few seconds due to difficulties in negotiating curves,
   - time spent in precisely positioning a source may not be of clinical consequence
   - margin of safety during bailouts and other emergencies.

Disadvantages-

1. Radiation protection concerns for all personnel.
2. Higher dose to surrounding normal tissues.
3. All treating personnel have to leave the patient during the radiation delivery.
4. Long dwell times.

2. *Beta emitters (e.g. Sr/Y-90, P-32):*

Advantages-

1. Minimal radiation protection considerations.
2. Short dwell times - fewer problems with ischemia during the dwell time.
3. Treating personnel can stay with patient at all times.

Disadvantages-

1. Steep dose gradient - relatively high dose to the intima for any dose prescribed into the vessel wall
2. The low energy may result in an under-dosing of adventitia.
3. Potential of "shielding", and consequent underdosing, due to stents, calcium or large plaques
4. Most pure beta-isotopes with energy adequate for intravascular applications have short half-lives (unless parent-daughter pairs are used).
5. The high dose-rates that can be achieved have the down-side of:
    i. Radiobiological disadvantage
    ii. Smallest alterations in the source delivery/retrieval times, especially in the manually operated systems, can result in potential over- or under-dosing, besides delivering relatively higher "in-transit" doses to normal tissues (though the absolute "in-transit" doses are quite insignificant).
6. The steep dose gradient also makes it preferable to have a centered system, especially in larger vessels, though the importance of centering in the coronaries is not yet clear.

The question of "gamma or beta" has been the subject of unending discussions and debates in the vascular brachytherapy community (8, 9, 10, 11). Despite these theoretical advantages and disadvantages of various gamma and beta emitting isotopes, it is important to realize that randomized clinical trials attest to the efficacy of both types of isotopes (12,13,14), indicating that appropriate use of the isotope may be at least important as the inherent physical properties.

Afterloading Systems in Brachytherapy (15)

The development of afterloading has contributed to a great extent to the renaissance of brachytherapy. The principle of afterloading is simple - unloaded tubes or applicators are inserted in the target volume, and these are subsequently loaded ("afterloading")with radioactive sources. Initially the afterloading was done manually. Later, in the early 1960s, the concept of remote afterloading was developed - here, the radiation sources remain in a shielded container and are inserted into the tubes/applicators via a remotely controlled afterloading device. Thus the radiation exposure to the operator is minimized.

Brachytherapy using remote afterloading can be delivered at a low dose-rate or high dose-rate. Depending on the dose that has to be delivered, in the low dose-rate (LDR) approach, the patient remained connected to the machine for several days. To facilitate nursing care and monitoring, automated units are available in which there is a mechanism to retract the sources back into the machine before anyone enters the room. In the high dose-rate (HDR) approach, similar devices are used, but a very high activity source is employed so that each treatment lasts only a few minutes.

Common Features of Most HDR Units (16)

The HDR unit consists of a mobile base that supports an enclosure for the necessary electrical components along with the source safe. Units typically weigh 100 - 250 kg. and have an

area of 1.5 sq. mts. The source safe is made of tungsten or depleted uranium and houses one or two 10.0 or 12.0 Ci. sources. The source drive mechanism consists of a stepping motor (Fig. 10.6) which moves the source in a few seconds from the safe to the applicator; then, under computer control, it moves the source through the applicator in a precise fashion, stopping for a variable amount of time ("dwell time") at different points along the applicator ("dwell positions"). The source drive mechanism is connected to the applicators via transfer tubes (source-guide tubes). Generally, HDR units have self-testing mechanisms to test applicator connectors. If the applicator connector fails, the source will not leave the unit or will automatically retract back into it. Iridium-192 is generally used as the source, due to its very high specific activity of 400 Ci/gm. This allows the source to be as small as 0.6 to 1.0 mm in diameter. One or more such cylinders or pellets of radioactive material are sealed inside a thin walled metal source capsule designed to absorb any undesired beta-rays. The diameter of the capsule is critical because the clinical situation may limit the size of the applicator tube that can be inserted into tissues, while the length of the capsule determines how acute a curve the source can negotiate. The source capsule is welded to a source drive cable which is driven by the source drive mechanism. It extends the source out of, and away from the machine; typical distances vary from 900 mm to 1500 mm. There is also a simulated (dummy) source or cable used to check the whole system and the source path; if the dummy cannot successfully negotiate the system, the real source cannot be used. The remote control unit

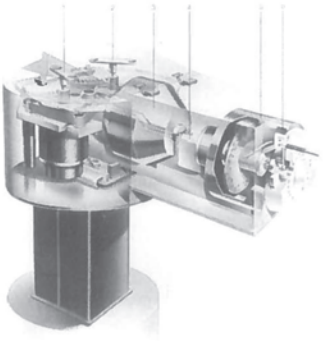


Figure 10.6: Interior of a typical high dose-rate remote afterloader, showing the source drive mechanism. Courtesy Nucletron Corporation

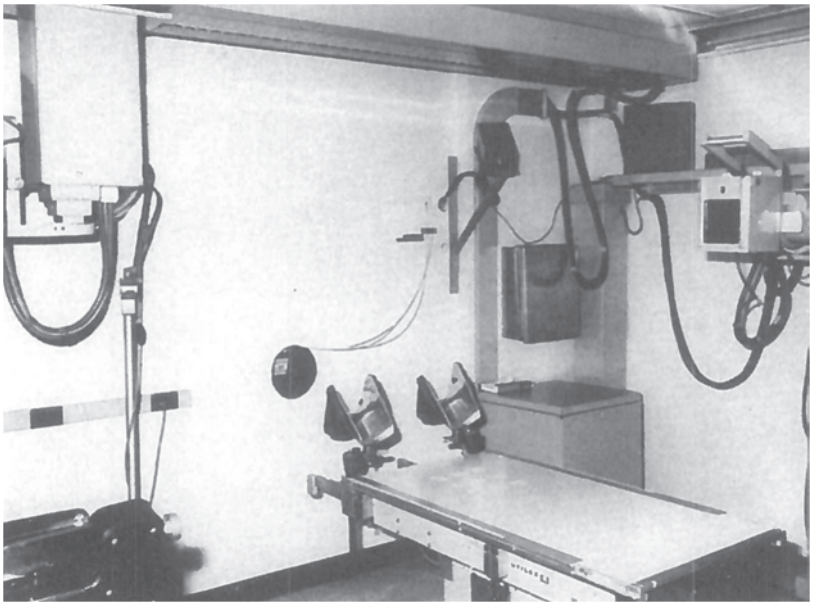


Figure 10.7 : Setup Of An HDR Suite. From: Hilaris B. Evolution and general principles of high dose-rate brachytherapy. In: Nag S (ed). High dose-rate brachytherapy: A textbook. Armonk NY: Futura Publishing Company; 1994. With permission.

stands outside the treatment vault and is usually a dedicated microprocessor that controls the HDR unit and the source movement. The information from the treatment planning computer (regarding the various dwell positions and the dwell times at each of these positions) is either directly transferred to the control unit via a serial cable or via programming cards.

Outline of a HDR Treatment Procedure (17)

Following the insertion of the applicators into the target volume, simulation X-rays are obtained with dummy wires placed within the applicators. The dummy wires have radiopaque markers along them at 1 cm. intervals. The desired volume to be treated is marked on the X-ray by the radiation oncologist, and this volume is digitized into a treatment planning computer. The actual dose and prescription point is decided. With this information, and the help of an optimization program, we can determine the optimal dwell positions, and dwell times at each position, along the applicator. This information is transferred to the remote control unit to regulate the source movements. The applicators are then connected to the HDR unit and the treatment delivered. Throughout the treatment, the patient and the HDR unit is monitored from outside the treatment vault by remotely operated video cameras, and there is an arrangement for two-way communication between the patient and the treating personnel (Figs. 10.7, 10.8).

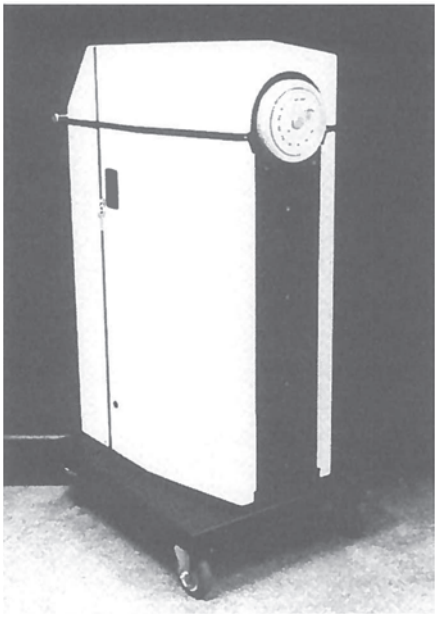


Figure 10.7a: Nucletron microSelectron

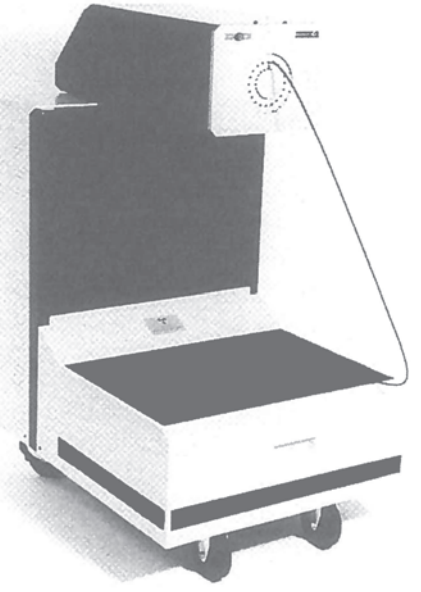


Figure 10.7b: Curietron

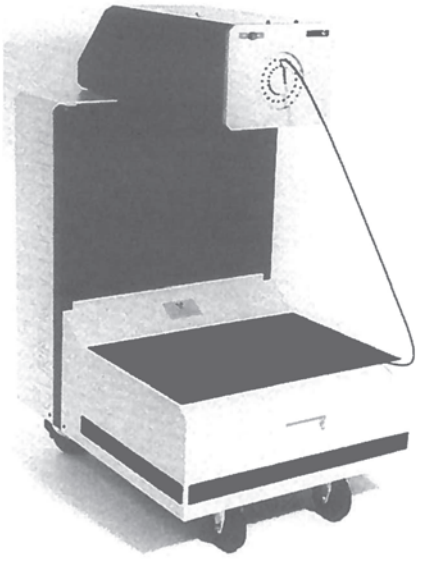


Figure 10.7c: Omnitron

Figure 10.7d: GammaMed

Figurel0.8a-d: High Dose-Rate Remote Afterloading Devices In Common Use. From: Glasgow GP, Anderson LL. High dose-rate remote afterloading equipment. In: Nag S (ed). High dose-rate brachytherapy: A textbook. Armonk NY: Futura Publishing Company; 1994. With permission.

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11

Basic Treatment Planning In Vascular Brachytherapy

Several important issues need to be taken into account when planning endovascular brachytherapy (EVBT) for preventing vascular restenosis. These include :

- Definition of the target
- Appropriate isotope
- Tandem lesions, Bifurcation lesions, Lesions in two separate vessels
- Effect of inhomogeneities, balloon materials, stents, contrast media
- Post-treatment evaluation
- Retreatment

Given the current state of endovascular brachytherapy, issues like retreatment, etc. may appear rather esoteric and theoretical. However, other issues, especially target definition and posttreatment evaluation, are of immediate relevance and need to be incorporated in daily practice to optimize the clinical results.

Target Definition

A clear definition of the radiation target is fundamental to the successful planning and implementation of any radiation therapy regimen. The term "target" is a 3-D concept, incorporating the length of the vessel to be treated as well as the depth into the vessel wall where the cells responsible for restenosis are believed to exist. There continues to be a lot of uncertainty regarding the precise vascular cells or the wall layer that needs to be targeted by the radiation therapy. A recent review of all the laboratory experiments concluded that the dose delivered at 0.75 mm into the vessel wall most closely correlated with the outcomes (1). On the other hand, failure analysis of the GAMMA-I study showed a distinct dose-response relationship based upon the dose that was delivered at 2 mm from the center of the source. Because of these uncertainties, the AAPM TG 60 recommended that the dose should be prescribed at a fixed distance of 2 mm from the center of the source in coronary applications; in the larger peripheral arteries, the corresponding dose prescription point should be the radius of the artery + 2mm (3). However, they also added that " ... for optimal assessment of each clinical case, average, minimum, and maximum doses delivered should be estimated in at least three planes perpendicular to the catheter and along its length." Based on these recommendations, current clinical trials specify the total prescribed dose at a specific radial distance (increasingly, the dose is being prescribed as per the TG 60 recommendations). However, few (if any) trials have clearly defined the length of the vessel that should be treated with the prescribed dose. It is not surprising that several of the major

trials -PREVENT, START, BRIE, to just mention a few - reported geographic misses of the order of 30 -50%.

Defining The Treatment Length

The importance of adequate treatment margins around the known extent of disease has been well known in radiation oncology for decades. In clinical radiation oncology, the radiation oncologist prescribes a therapeutic dose to the known extent of malignant disease along with an adequate margin for various uncertainties inherent in the treatment planning and delivery process. Based upon this, the International Commission on Radiation Units and Measurement (lCRU) recommendations for treatment planning volumes can be summarized as follows: (1) Gross tumor volume is the gross palpable or visible/demonstrable extent of the malignant growth; (2) Clinical target volume includes gross tumor volume plus regions considered to harbor potential microscopic or sub-clinical diseases; (3) Planning target volume is the clinical target volume plus a margin to account for the uncertainty regarding patient and organ motion during treatment; (4) Treatment volume is the volume that needs to be "treated" in order to ensure that the planning target volume receives the prescribed dose (this usually incorporates the planning target volume plus a margin to account for beam penumbra i.e., fall-off of radiation dose at the edge of the field). The treatment volume is the volume enclosed by an isodose surface, and is selected and specified by the radiation oncologist (4) As a direct extension of these guidelines, Tripuraneni, Parikh et al proposed the following definitions for EVBT (5):

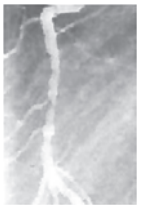

Figure 11.1 : GTL Courtesy Dr. Prabhakar Tripuraneni, Scripps Clinic, LaJolla, CA.

1) Gross Target Length (GTL) is defined as the length of the narrowed segment of the artery which requires intervention. In clinical practice, the GTL is usually determined from the diagnostic angiogram, though intravascular ultrasound (lVUS) may be useful in selected cases.

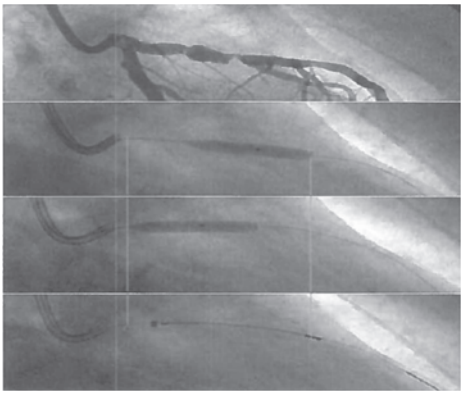

Figure 11 .2 : Deriving the CTL - note multiple balloon inflations, and the extension of the CTL beyond the initially stenotic segment. Courtesy Dr. Prabhakar Tripuraneni, Scripps Clinic, LaJolla, CA.

2) Clinical Target Length (CTL) is defined as the length of vessel that is "injured". This "injury" could be due to the angioplasty, atherectomy, stenting, or stent deployment. It is important to appreciate the distinction between the injury caused by the stent and that caused by stent deployment. The former results from the

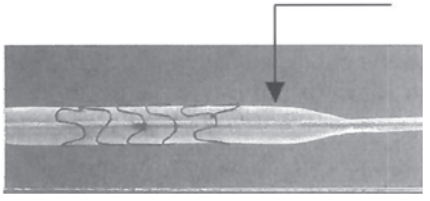

Figure 11.3 : Barotrauma due to the stent deployment balloon - note the shoulders of the balloon extending beyond the ends of the stent.

actual stent struts as they project into the vessel wall, while the vessel injury from the stent deployment is due to the balloon (barotrauma) utilized to position the stent within the vessel. The shoulders of the balloon extend beyond the ends of the actual stent, resulting in an extension of the "injury" zone beyond the ends of the stent. Review of current FDA-approved stents shows that the length of the deployment balloon is 2 to 6 mm longer the stent length; in another word, the most distal and proximal extent of injury due to the deployment balloon lie 1 to 3 mm beyond the stent edge (6).

3) Planning Target Length (PTL) incorporates the CTL plus a margin on either side to account for heart/catheter movement, source drift and uncertainty in target localization (thus, the CTL can be visualized as moving within the "envelope" of the PTL, while being constrained by the margins of the PTL). The heart/catheter movement and source drift refers to displacement of source and catheter relative to the vessel. Data from the Scripps Clinic indicates that this depends on the location of the lesion within the vessel (more for proximal than distal lesions), delivery systems (more for non-centered than balloon-centered catheter systems), and the cardiac status (ejection fraction, cardiac hypertrophy, etc.) The actual magnitude of this displacement ranged from 0.4 mm to 5.4 mm (7). This translates into a margin of 3 to 5 mm (mean plus 2 standard deviations) for a typical non-centered delivery system. The uncertainty in target localization refers to the inaccuracies inherent in trying to pinpoint CTL and precisely position the source train in relation to this CTL. Multiple balloon inflations, "touch-up inflations" to optimize stent deployment, etc. can accentuate this uncertainty.

4) The Treatment Length (TL) is the actual length of the source train required for the treatment. This is the PTL + a margin for the penumbra effect. In EVBT, the penumbra is defined as the distance from the source end to the prescribed isodose line measured at the distance from the source train at which the dose is prescribed (and not along the long axis of the source train itself). It is important to realize that along the long axis of the source train, the length of prescribed isodose does not end at the end of the source, but extends beyond both source ends for a variable distance. However, what is of real interest is the length of the prescription isodose (in relation to the length of the source train) at the prescribed distance from the source train (e.g. 2 mm). This is the length that is really available to us for treating the PTL; it is always shorter than the source train length because, as we move away from the source train (in a radial direction), the isodoses "bow inwards", i.e. they curve towards the source train as one approaches the ends. Thus if the source train length (Treatment Length) were selected to be exactly equal to the Planning Target Length (i.e. the length of the vessel that we wanted to treat to a given dose), the ends of that vessel length would be underdosed. This is because, at the treatment distance (i.e. at the level of the

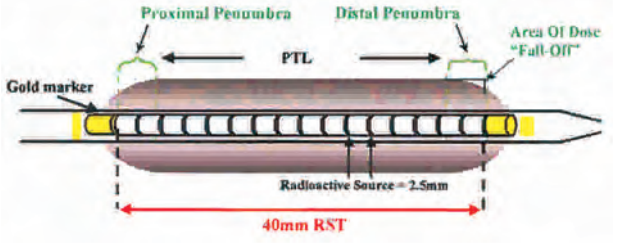

Figure 11.4 : lllustration of the penumbra effect with a line source - note the curving of the isodose surface at the ends of the source train and the area of "dose fall-off". Courtesy Dr. Raoul Bonan, MD and Novoste Corporation.

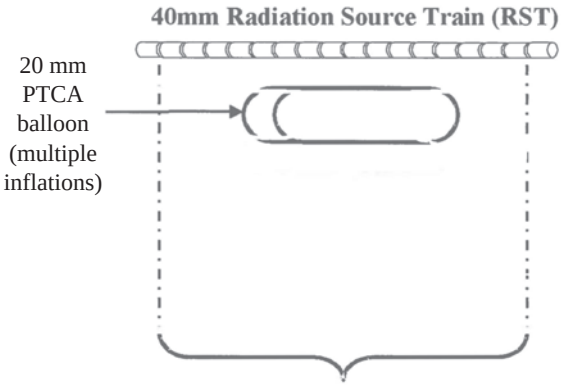

Figure 11.5 : Derivation Of The Final Treatment (Source Train) Length. Courtesy Dr. Raoul Bonan, MD and Novoste Corporation.

prescription isodose, say 2 mm), points in the central portion of the PTL receive radiation not only from the source in direct line with that point, but also from the 2-3 sources on either side of that source. It is easy to appreciate that as one moves to the end of the PTL (at the prescription distance), the terminal points along the PTL can receive radiation only from the source directly in line with that point, which translates into a lower dose compared to the central points, and consequent "curving inwards" of the isodose lines (Fig. 11.4). The penumbra effect depends on source isotope, uniformity of activity along the source train length, source design, and the prescription distance (8, 9). This penumbra effect requires the addition of an additional margin to the PTL to determine the final length of the source train that is required to adequately treat the CTL. In other words, the treatment length, or the required length of source train, is equal to the length of PTL plus the penumbra (Fig. 11.5).

Selection of Isotope

The characteristics of an "ideal" isotope for endovascular brachytherapy, and the relative advantages and disadvantages of gamma- and beta-emitting isotopes have already been discussed. Despite the extensive animal and clinical work in this field, there continues to exist an uncertainty regarding the precise layer (or cells) of the arterial wall that need to be targeted with the radiation. Similarly, there is little data to indicate what constitutes an appropriate radiation dose (some preliminary data from the GAMMA-I study would indicate that a minimum of 8 Gy should be delivered at 2mm from the source axis to observe any benefit from the radiation therapy). And finally, there is no data to suggest what is a "safe" radiation dose (the absence of true long-term follow-up, the small volumes of tissue involved, the potential errors in dosimetry at such close ranges and the very steep dose gradients all collude to make this estimation even more difficult). In the clinical setting, the magnitude of uncertainty introduced, as a result of these factors, almost trivializes any attempts to judge the relative advantages and disadvantages of gamma- Vs. beta-isotopes in the context of issues such as source centering, presence of inhomogeneities, shielding by stent struts, dose rate effects, etc.

If one were to consider only the issue of *short-term efficacy,* the available clinical data seems to suggest that gamma-emitters like Ir-192, and beta-emitters like Sr-90, Y-90 and P-32 all seem to work equally well. The trial's data also highlights that meticulous implementation of the

radiation therapy (in terms of margins, depth of dose prescription, etc) is probably much more important in determining the final outcome than differences in the isotopes used (thus, P-32 as a radioactive stent has not shown to "work", mainly because of the problem of edge failures, while the same isotope, when appropriately used in catheter-based systems, e.g. the Guidant Galileo System, appears to be quite effective).

Tandem Lesions, Bifurcation Lesions and Multi-vessel Disease

These situations present special treatment planning challenges. Atherosclerosis is a generalized process and multiple lesions and multi-vessel disease are common clinical problems. The anatomy of the coronary arterial tree (and the separation between the major branches) does not pose any special problems in treatment planning for multi-vessel disease. The vessels are usually far apart such that, in most instances, there is little danger of overdosing the watershed area in between the two vessels. Because of the rapid dose fall off, beta-emitters may be advantageous in this setting. The BRIE and RENO studies, in Europe, are evaluating the use of the Novoste device in multivessel disease.

Tandem lesions present a slightly greater challenge. However, provided the two lesions are separated by a gap that is long enough such that (along the central axis of the source) the 50% isodoses of the two treatment lengths either just abut with each other (maximum dose at interface = 100%) or are actually separated, the two lesions can be managed by treating them sequentially, without any danger of overdosing the intervening gap. Obviously, precise positioning of the sources is the key to avoiding any complications in this already "complex" situation. For any PTL, the "penumbra effect" is somewhat shorter with a beta-emitter (when compared to a gamma, mitter) (8); accordingly, beta-isotopes may once again be slightly advantageous in this setting. On the other hand, the beta isotopes are already associated with a much higher intimal dose, so that there is a very small margin of safety in case of any inadvertent "overlaps". An automated, programmable remote afterloader with a stepping source would obviate these problems.

Bifurcation lesions are particularly challenging to treat with the current available technology. Even with the most meticulous of pre-treatment planning, depending on the angle of the "carina" between the two branches, there is always the potential of under- or overdosing the vessel wall at the bifurcation. Once again, the steep dose gradients associated with the beta sources would appear to be potentially advantageous in this situation. However, this may not hold true if the adventitia is actually the radiation target. Development of programmable afterloaders with a stepping source would again provide an elegant solution to this problem.

Effect of contrast media, plaque and other inhomogeneities

In intravascular brachytherapy, the interposition of high atomic number media, in the path of the radiation beam, can introduce significant dose pertubations in the medium. Nath et al (10, 11, 12) have done extensive modeling to study the effects of inhomogeneities such as contrast media, calcific plaque, and metallic stents on the dose-distribution from various intravascular brachytherapy sources. They studied the effects at the immediate tissue-inhomogeneity interface, the distance over which this effect was manifest and the "shielding" caused by the interposition of such inhomogeneities. Their results can be briefly summarized as follows:

The dose enhancement factor (DEF) was defined as the ratio of the peaked dose at the interface between water and the inhomogeneity (high atomic number material) to the dose at the

corresponding location without the interface. The DEF increased with increasing photon energy and then decreased as the photon energies were further increased in the model. At 20 keV, the DEF ranged from 2.5 to 8.5. The DEF reached a peak at a photon energy of about 60 keV, and the actual values of the DEF were 18.3, 18.7, 19.1 and 3.1 for Hypaque, Omnipaque, stainless steel and calcific plaque, respectively. As the photon energy increased to 200 keV, these values dropped to 2.2, 2.5, 1.5 and 1 respectively. In the whole range of energies studied by the authors, the maximum DEF for the calcific plaque-water interface was 4.5, and dose pertubations introduced by the presence of a plaque were much less than those caused by the other inhomogeneities that were studied. Above 200 keV, the magnitude of dose pertubation was negligible.

The dose enhancement distance (DED) was defined as the distance from the interface at which the dose with the existence of the high atomic number inhomogeneity was at least twice the dose without the presence of the inhomogeneity. The DED was related to the photon energies in a more complex fashion. However, for calific plaques, the DED increased with photon energies, and then decreased at a photon energy of about 70 keV. More importantly, the range of the absolute values for DED were very small: 1.3 microns for 20 keV, increasing to about 70 microns at 100 keV. Thus, the dose pertubations caused by the inhomogeneities were limited to a very short distance of ≤ 0.1mm.

When the shielding effects of various inhomogeneities were studied by looking at the dose rates at 2 mm from the source, none of the materials affected the dose rate delivered by photon sources with energies greater than 100 keV. On the other hand, low energy photon sources (e.g. I-125, Pd-103) were significantly affected by these inhomogeneities - thus dose beyond a 1 mm thick plaque was reduced by about 17% for I-125 and 43% for Pd-103. Similarly, for beta sources, the penetration depth was reduced by all the inhomogeneities studied (in contrast to the photon sources, the inhomogeneity reduced the *depth of penetration* of the beta sources; merely increasing the activity or the dwell time would not compensate for this effect).

The interested reader is referred to the original articles for further details.

Post-treatment Evaluation

Post-treatment evaluation will become increasingly important, once endovascular brachytherapy emerges from the "experimental" realm and becomes a part of clinical practice. While the simplest post-treatment evaluation could consist of superimposing a set of isodose curves onto a representative angiogram frame that shows the source in position, this is not likely to provide any meaningful information. At the minimum, post-treatment evaluation should consist of a display of the dose-distribution in relation to cross-sectional IVUS images, such that estimates can be made of doses delivered to the various layers (? thicknesses) of the arterial wall. The ideal would probably be a three-dimensional reconstruction of the target volume (from lVUS data), with the dose-distribution being displayed as a dose-volume histogram; this would incorporate inhomogeneity corrections to account for the varying attenuation properties of plaques and other inhomogeneities that are present in the volume under consideration. Prototypes of such evaluation systems are under evaluation at the Emory University in Atlanta, GA and at the Dr. Daniel den Hoed Cancer Center, Rotterdam (13, 14). All this would only be possible if intravascular brachytherapy evolved as an image-based radiation therapy application, which used some cross sectional imaging modality (most probably lVUS) to plan dose prescription and post-procedure evaluation.

Re-treatment

For any "re-treatment" situation, it is very important to be able to have access to all prior radiation therapy records. If adequate documentation is available, treating another vessel, or a different lesion in the previously treated vessel should not be a problem. However, there is almost no good long-term clinical data regarding the late effects of endovascular radiation, and it is rather premature to consider the issue of re-treating patients who have "relapsed" at the same site after prior endovascular brachytherapy (i.e. a target lesion failure). With that caveat in mind, there may be very selected situations in which such a re-treatment may be considered. Patients who experience an "edge failure", due to inadequate margins at the initial treatment, may be considered as potential candidates for re-treatment. It would be mandatory to have access to the complete angiographic record from the prior therapy to establish the current problem as a true "edge failure" and re-treatment should only be considered if the length of "overlap" is quite short - in reality, this may be difficult to achieve, because of the necessity for adequate margins on either side of the lesion.

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12

Clinical Applications Of Vascular Radiotherapy Coronary Applications

Post-angioplasty coronary restenosis is a major clinical problem. With the exception of intracoronary stents, mechanical and pharmacological adjuncts have had little impact on the natural history of this process. Unfortunately, population demographics predict a continued rise in the incidence of coronary artery disease, with a concurrent increase in the number of coronary interventions performed annually. In 2000, over 750,000 coronary angioplasties are likely to be performed in the United States alone. Assuming a stent usage of about 80% and a conservative instent restenosis rate of approximately 20%, this translates into an annual incidence of more than 100,000 cases of in-stent restenosis. This is rapidly growing subset of patients is, especially refractory to conventional therapies. The management of post-PTCA restenosis underwent a major paradigm shift with the appreciation of restenosis as a growth disorder; this culminated in the development of endovascular brachytherapy. Following the pioneering laboratory work and clinical studies of Waksman, Weinberger, Tierstein and others, several innovative approaches have now been developed for the delivery post-angioplasty radiation. These approaches can be broadly divided into :

1) Catheter based radiation therapy approaches

Catheter-based approaches have been widely used in clinical trials. The segment of the artery that is "injured" by the intervention is spanned by a closed-ended catheter. The radiation source is "transported" through this catheter to the target site, and is maintained at this site to deliver the prescribed dose. The devices differ in the radioactive isotope (Ir-I92, Sr/Y-90, Y-90, P-32, Re 186/188), the configuration of the isotope (seed train, wire, coil, etc.), the delivery system (manual, mechanical, hydraulic or remote-controlled) and whether or not a centering balloon is used. Despite these differences, the catheter-based approaches have yielded the most consistently positive results.

2) Radioactive liquid/gas filled balloons

In this approach, the "injured" coronary segment is spanned with a balloon catheter, and the balloon is inflated with a radioactive isotope for the prescribed time. Common isotopes evaluated include Re^{188} - RADIANT™ (Progressive Angioplasty Systems, Menlo park, CA, USA), and SABER (**S**olution-**A**pplied **B**eta-**E**mitting **R**adioisotope) / CURE (Columbia University Radiation Energy) Systems, Re^{186} - RadioCath™ System (Mallinckrodt Inc. St. Louis, MO, USA), Ho-166, Cu-62, and Xe^{133} - XenaCath™ System (Cook Corporation, Bloomington, IN, USA). The concept has some dosimetric advantages because of the inherent "centering" of the source and the uniform apposition of the balloon/source with the vessel surface, even in the

presence of vessel curvatures and angulations. However, there are several real and potential problems which may limit the widespread successful use of these systems. These include the relatively "less penetrating" beta-radiation from some of these isotopes, logistical issues involved in synthesis and supply of the isotopes, and the ever-present danger of a radioactive spill with contamination of the catheterization laboratory and/or personnel. Balloon rupture within the patient is also a real cause for concern, though the rhenium isotopes can be "designed" to be rapidly excreted via the kidney, the copper isotope has a very short half-life (9.7 minutes), and xenon would be exhaled out without any danger to the patient or the environment.

3) Radioactive stents

The vast majority of coronary interventions involve stenting, and using the stent as a radiation delivery platform has obvious advantages. Conceptually, this would be the simplest approach for intracoronary radiation. Stents can be made radioactive by at least three different processes: a) bombardment of metallic stents with protons or deuterons, e.g. deuteron bombardment of stainless steel Palmaz Schatz stents, and the proton bombardment of nitinol stents, b) coating the stent surface with the selected isotope, and c) ion implantation of the selected isotope onto the stent surface by the selected radioisotope, most commonly P-32 (though other isotopes, including Pd- 103, Au-I92, etc. are being studied). Ion implanted P-32 has been widely evaluated in association with Palmaz Schatz and BX stents. Unfortunately, the initial clinical trials failed to deliver the benefits that radioactive stents had promised in the animal studies (1, 2). Radioactive stents have been very effective in neointimal inhibition within the body of the stent, but all clinical trials have been plagued by an unacceptable incidence of restenosis at the stent edges. A variety of rather fanciful terms, like the "candy wrapper effect", (3) have been coined to describe this distinctive angiographic appearance. Several innovations have been tried to minimize these edge failures. High activity stents have been used to try and increase the dose at (and beyond) the stent ends. Similarly, "gentler" balloon inflations, using balloons with minimal "shoulders", have been tried in an effort to precisely limit the zone of "injury" to the stented segment. Despite all these, edge failures continue to be a significant problem, negating any potential advantage from the elimination of the neointimal proliferation within the body of the stent itself (4).

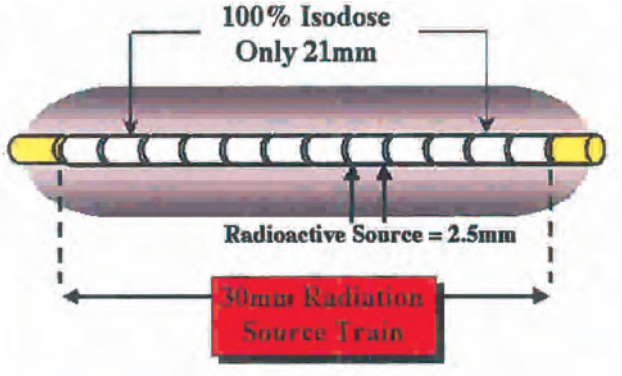


Figure 12.1: Dose distribution around a radioactive line source (RLS) showing the in-bowing of the prescription isodose (at 2 mm) as we approach the ends of the source - at 2 mm distance a length of only 21 mm receives the prescribed dose from this 30 mm long RLS.

This lack of success is quite simply explained by the basic physics of a radioactive line source. Along the long axis of a radioactive line source (RLS), the prescribed isodose extends beyond both source ends for a variable distance. *However, what is of real interest is the length of the prescription isodose (in relation to the length of the RLS) at the prescribed distance from the RLS.* This is the length that is really available for treating the "injured segment" of the artery. This length is always shorter than the RLS length because, as we move away from the RLS (in a radial direction), the isodoses "bow inwards", i.e. they curve towards the RLS as one approach the ends (Fig. 12.1). Thus, if the RLS length were selected to be exactly equal to the "injured vessel length" that we wanted to treat to a given dose (as is the case with the radioactive stent), *the ends of that vessel length would always be under-dosed, with the consequent edge failures* (5).

Newer stent designs are attempting to "differentially load" the stents (such that there is a higher activity at the two ends - the "hot ends" approach) in an attempt to address this problem in the future.

4) Radioactive balloons

This innovative approach (the "hot balloon" concept) employs a special tri-Iayer balloon in which a radioactive isotope (P-32) layer is "sandwiched" between two membranes constituting the wall of the balloon - RDX™ Radiation Delivery System (Radiance Medical Systems, Irvine, CA, USA). Inflation of the balloon brings the isotope in close, and uniform, apposition with the vessel wall. This is a simple and elegant concept. However, the half life of P-32 is only 14 days and maintaining an inventory of several different balloon lengths with sufficiently high activity, makes this a logistically challenging procedure. Furthermore, the close apposition of the source to the luminal surface results in a steep transmural dose-gradient, with a high luminal/endothelial dose for any given dose at a depth into the vessel wall.

5) Other approaches

These include the IRRADIATOR™ (Interventional Technologies, San Diego, CA, USA) system which tries to "infiltrate" liposome-encapsulated radioactive 99-technetium into the vessel wall at the site of the balloon injury by using a specially designed intramural drug delivery balloon (the "hot artery" concept), a radioactive expandable metallic mesh (which is used to "recanalize" and radiate the stenotic segment), the use of low power red light laser, photodynamic therapy, sonotherapy and even very soft X-rays which are generated and delivered by a cable system directly to the angioplasty site (6).

The catheter-based therapies have been widely used for almost 5 years. More than 5000 patients have been treated in several clinical trials, and some of these systems are already commercially available outside the United States. Based on the consistently positive results from clinical trials, the FDA Advisory Panels have already approved two systems - the Cordis Ir-192 Checkmate™ system (Cordis Corporation, Miami, FL, USA), and the Novoste Sr/Y-90 Beta-Cath™ System (Novoste Corporation, Norcross, GA, USA); the FDA is expected to "clear" them for marketing within the United States by the end of this year. The remainder of this chapter will focus on the catheter-based systems, since the other devices are still quite "experimental".

Endovascular Brachytherapy Employing Manually After-loaded "High Activity" Iridium-192

This was the fIrst clinical application of intracoronary brachytherapy in humans. Condado et al (7) treated 21 patients (22 arteries) in Venezuela with a 3 cm. long, 529 - 982 mCi. Ir-192

source (outer diameter of 0.014" - 0.018"). Following a successful intervention, a 4 Fr. catheter was positioned at the presumed site of "injury", and the catheter was manually afterloaded with the Ir- 192 source. A dose of 20 or 25 Gy was prescribed at a distance of 1.5 mm from the source. At 12 months clinical follow-up, 80.9% patients remained free of myocardial infarction, bypass surgery or target lesion revascularization (TLR). Being a non-randomized, feasibility and safety study, it is difficult to comment on the clinical efficacy of the procedure. However, the retrospective dosimetric analysis is very instructive, since it highlights the potential problems that can arise with the use of a non-centered source. Despite prescribed doses of 20 or 25 Gy, the calculated doses at the luminal surface ranged from 19.5 Gy to 55 Gy while the dose at the reference vessel diameter varied between 11.1 Gy to 42.9 Gy. In the group of patients with a prescribed dose of 25 Gy, the eccentric lie of the catheter resulted in a potential dose variation from a high of 92.5 Gy (when the catheter lay against the vessel wall) to a low of 7.2 Gy (at the contralateral wall). It is possible that these doses contributed to the angiographic complications seen in 6 out of the 10 arteries that were treated with a prescribed dose of 25 Gy (2 total occlusions, and 4 vessels with pseudoaneurysms &/or arterial dilatations). Overall, though, the results in this small group have been very durable out to a follow-up of almost 4 years. The obvious problems of radiation exposure with the use of such a high activity source preclude its routine use.

Iridium - 192 Seed Trains - The Cordis Checkmate™ System

The Cordis Checkmate™ system is a very simple manual after-loading system. It consists of the Checkmate™ Radiation Delivery catheter and the radiation "pig" which serves as a radiation source storage and delivery device. The radiation delivery catheter has evolved over the years and is currently a 3.7 Fr catheter with a single, closed lumen for the radioactive source and a very short distal monorail (Fig 12.2). The distal end of the closed lumen is marked by a radiopaque marker. This allows visualization of the distal end of the source lumen, and thus ensures that the radiation source is advanced to the end of the source lumen. The catheter is supplied "preloaded" with the dummy ribbon within the source lumen. This dummy ribbon has inactive seeds and radioopaque markers which bracket the different lengths of the radioactive sources (Fig. 12.3). The dummy ribbon "stiffens" the radiation delivery catheter, aiding its advancement into the coronary artery. It also serves as a "measuring tool" to estimate the length of the arterial segment that is "injured" and thus aids in selecting the appropriate length of the radiation train, while allowing for precise positioning of the radiation delivery catheter across the "injured" arterial segment. The radiation source consists of a nylon ribbon (Fig.12.4, 12.6), outer diameter of 0.030", that "houses" the Ir- 192 seed train (Best Medical International, Springfield, VA); each seed has an initial activity of 33 mCi. Seeds are 3 mm long (Fig. 12.5), with 1 mm inter-seed spacing .

Figure 12.2: The Checkmate™ Radiation Delivery Monorail Catheter. Courtesy Cordis Corporation.

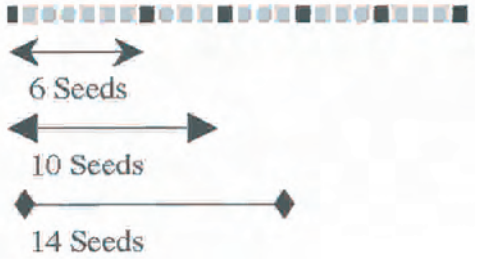


Figure 12.3: Schematic of the "dummy" ribbon

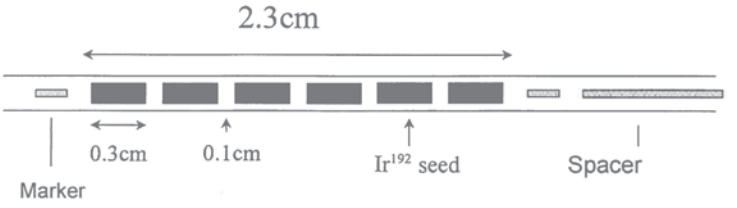


Figure 12.4: Schematic of the Source Ribbon (From Jani S, Huppe G et al. BEST: Manually Loaded Iridium 192 Ribbon. In: Waksman R. ed Vascular Brachytherapy, 2nd Ed. 1999. Armonk, NY: Futura Publishing Company, with permission)

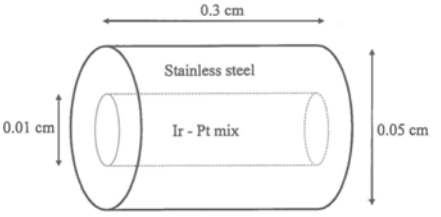


Figure 12.5: Schematic representation of an Ir-192 seed (From Jani S, Huppe G et al. BEST: Manually Loaded Iridium 192 Ribbon. In: Waksman R. ed. Vascular Brachytherapy, 2nd Ed. 1999. Armonk, NY: Futura Publishing Company, with permission)

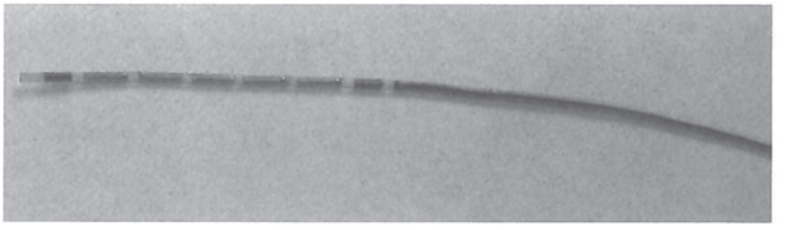


Figure 12.6: Ir-I92 Source Ribbon (From Jani S, Huppe G et al. BEST: Manually Loaded Iridium 192 Ribbon. In: Waksman R. ed. Vascular Brachytherapy, 2nd Ed. 1999. Armonk, NY: Futura Publishing Company, with permission)

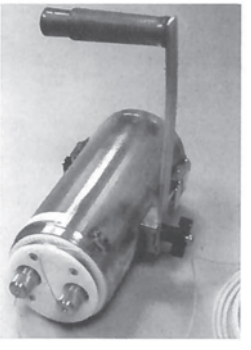


Figure 12.7: "Pig" for storage and transportation of radiation source ribbon. (From Jani S, Huppe G et al. BEST: Manually Loaded Iridium 192 Ribbon. In: Waksman R. ed. Vascular Brachytherapy, 2nd Ed. 1999. Armonk, NY: Futura Publishing Company, with permission)

Figure 12.8: Radiation source being advanced into the radiation delivery catheter (From Balter S. Endovascular Brachytherapy: A Health Physics Perspective. In: Waksman R. ed. Vascular Brachytherapy, 2nd Ed. 1999. Armonk, NY: Futura Publishing Company, with permission)

The source is stored in a cylindrical lead "pig" which has a luer lock connection on one end plate (Fig. 12.7). This luer lock is connected securely to the catheter and the ribbon is manually afterloaded into the radiation delivery catheter by pushing the "tail" of the source that emerges from the opposite endplate of the "pig" (Fig 12.8).

Figure 12.9: Example of a mobile brachytherapy shield

It is left there for the prescribed dwell time, following which it is pulled back into the protective "pig". The manual loading takes approximately 10 seconds, and retrieval is achieved in less than 5 seconds. Manual afterloading provides excellent tactile feedback to the operator, especially while negotiating angulations and curves within the coronary artery. The dwell times vary from 15 - 20 min. depending on the activity of the source (Ir-l92 decays by about 1 % of its activity every day, and the source is exchanged every 30 days to avoid prolonged dwell times). To minimize radiation exposure, only the radiation oncologist and physicist remain in the room with the patient when the source is loaded and unloaded (no one remains in the room during the actual dwell time). A long intravenous line is brought out into the control room to allow for delivery of medications, if required. Special mobile brachytherapy shields (Fig. 12.9) are also placed along side the patient to minimize radiation exposure within the control area and the adjoining rooms.

This system was fIrst successfully used in the landmark SCRIPPS (Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting) trial at the Scripps Clinic & Research Foundation. SCRIPPS was a double-blinded, randomized placebo-controlled trial evaluating the role of post-angioplasty endovascular brachytherapy in patients with coronary restenosis (8). Sixty patients were enrolled. These patients had a particularly poor prognosis as evidenced by the fact that they had an average of 2 interventions prior to entry into the protocol; about 35% were diabetics, 30% had vein graft stenosis and about 30% had ostial lesions. Following an adequate PTCA (+/- stenting) of a restenotic lesion in a native vessel or vein graft of at least 3 mm diameter, a motorized IVUS pullback was performed to obtain a baseline post-PTCA minimal luminal diameter, as well as to obtain data for dose prescription and dosimetry. On successive IVUS images, the shortest and largest distances from the IVUS catheter to the media-adventitia interface (external elastic lamina) were measured. The goal was to deliver 800 cGy to the furthest point on this interface, while ensuring that none of the interface received > 3000 cGy (Fig.12.10). The lesion was then spanned with a 4 Fr catheter (the original catheter was actually openended, but was soon replaced by a close-ended catheter) that was meticulously positioned to "cover" the injured segment of the

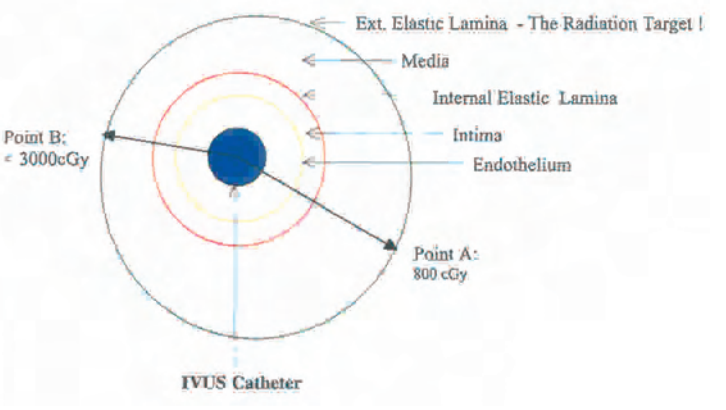


Figure 12.10 : Schematic of dose prescription in the SCRlPPS Trial

artery. The treated segments were less than 25 mm in length. The dwell times varied from 27 - 43 min. with a mean of 35 minutes. (Patients randomized to the placebo arm were treated with an identical ribbon with non-radioactive seeds). Throughout the procedure, a heparin infusion was maintained through the 4 Fr. catheter. All patients had a six month follow-up angiogram and IVUS study, and these were independently evaluated at off-site core laboratories by observers who were blinded to the treatment arms.

At 6 months follow-up, the binary angiographic target lesion restenosis rate (> 50% narrowing) of the stented segment + a 5 mm margin on either side was only 17% in the irradiated group vs. 54% in the control; if the marginal failures were excluded, the differences in in-stent restenosis rates were even more marked, 8% vs. 36%. Similarly, at a mean follow-up of 12.2+/-2.9 months, only 11.5% of the treated group needed TLR (target lesion revascularization), vs. 45% in the control, while only 15% required "any lesion revascularization" in the irradiated group vs. almost 60% in the controls (Fig. 12.11). Quantitative coronary angiography (QCA) showed that there was no difference in the stent volumes in the two groups; however, the lumen volume in the controls was only 16 +/-24 cu mm Vs. 44.3+/-34.6 cu mm in the irradiated patients, indicating an absence of neointimal encroachment on the lumen. Similarly, the late lumen loss was only 0.38 mm in the irradiated patients compared to an average of 1 mm in the controls; this translated to a late lumen loss index of 0.12% for the treated group vs. 0.6% for the controls (8). Though the numbers were small, the differences were even more marked in the subgroups of diabetics, those with arteries <3 mm and in patients with vein graft stenosis - all subgroups with a known bad prognosis (9). These results have continued to hold true even at a follow-up of 36 months (Fig.12.12), indicating the durable nature of the restenosis-inhibition that was achieved with this approach (10).

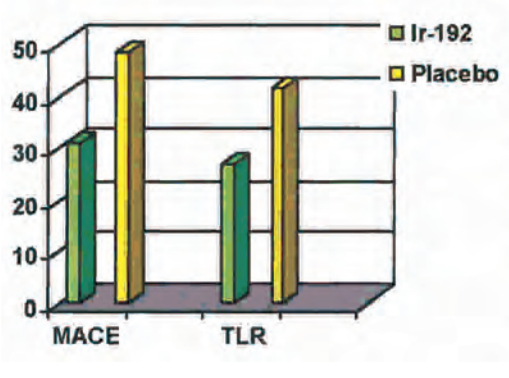


Figure 12.11 : SCRIPPS - Clinical F.U. At 3 years

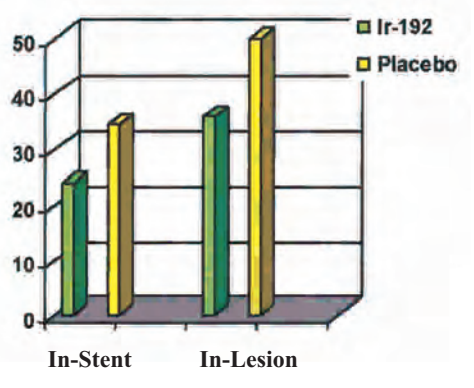


Figure 12.12 : SCRIPPS Angiographic Restenosis at 3 years

This approach has been criticized because of :

1) Prolonged treatment times
2) Potential for radiation exposure to the treating personnel.
3) Need for special shields
4) Treating personnel cannot remain in the room with the patient during the treatment.
5) "Excessive" dose to the vessel wall, heart and adjoining normal tissues.

However, in reality :

1) The "long" treatment times are a reflection of a relatively "low dose-rate". This can actually be advantageous where :
   i) There is difficulty in delivering the source to the target site (due to tortuosity/kinks);
   ii) There is an inadvertent prolongation of the treatment time by a few seconds; or
   iii) Repositioning of the source is required to accurately span the target length of the vessel.
2) The main source of radiation exposure to the catheterization laboratory personnel is the fluoroscopy and cineangiography. During the brachytherapy procedure, all personnel are in the control room , behind the shields and receive, on an average, < 0.5 micro Sv per case. The radiation oncologist and radiation physicist are the only personnel receiving any significant exposure - 10 micro Sv and 7 micro Sv per case, respectively (11) - and even this is no more than the dose received in an average oncologic brachytherapy procedure.
3) While it is true that no one can stay in the room with the patient, the patient is continually observed and monitored from the control room. The patient and the medical team are able to verbally communicate with each other, and medications can be delivered to the patient via the long intravenous line that is brought out into the control room. In the event of significant chest pain or hemodynamic instability, the procedure can easily be fractionated.
4) The purported "high" doses to the heart and normal tissues are a function of the high gamma energy of Ir-192. However, this high energy gamma output has several theoretical advantages:
   i) A shallow dose gradient, ensuring a relatively low intimal dose for any given prescription dose to the media-adventitia interface.
   ii) The high energy gamma radiation reduces the likelihood of underdosing the target despite some degree of off-centering, or presence of plaques, calcifications, stents, etc.
   iii) In reality, the majority of the dose to the heart and adjoining normal structures is delivered from the fluoroscopy and cineangiography - the brachytherapy contributes little additional clinically relevant dose. Thus, a dose-volume analysis at the Scripps Clinic showed that less than 6 cc of the myocardium received ≥ 180 cGy (S Jani, personal communication), while estimates of doses to the adjoining normal structures revealed the following:

Table 1

Dose to adjoining normal structures with the Cordis Checkmate™ System
(Albert Sabbas, PhD, New York Presbyterian Hospital, Cornell campus, New York, NY)

Source Configuration	Total Activity	Lung (rads)	Skin (mrads)	Marrow (mrads)
6 seeds	192 mCi	12	0.16	0.41
10 Seeds	320 mCi	20	0.27	0.68
14 Seeds	448 mCi	28	0.38	0.95

This study evolved into the **GAMMA-I** Study, which was a multi-institutional trial designed to evaluate the procedure in 252 patients from 12 different sites within the United

States. Patients with in-stent restenosis of native coronary arteries, reference vessel diameter 2.75 - 4.0 mm, lesion length ≤ 45 mm, were enrolled. Source trains were available in three lengths - 6 seeds, 10 seeds and 14 seeds - translating into active lengths of 23 mm, 39 mm and 55 mm respectively.

Dose prescription employed IVUS and was similar to the SCRIPPS trial. Clinical and angiographic follow-up revealed a very similar benefit from radiation. At 6 months angiographic follow-up, there was a 43% reduction in the target lesion restenosis rate - 32% in the irradiated group Vs. 55% in the control. If the marginal failures were excluded, the outcomes were even more impressive - there was a 58% reduction in the in-stent restenosis rate, 21 % Vs. 50.5%. Similarly, at 9 months clinical follow-up, there was a 38% reduction in the incidence of the composite clinical endpoint of MACE* in the irradiated patients (29% Vs 46%) and a 42.5% reduction in the number of patients needing a TLR - 25.2% in the treated group Vs. 44% in the control (Fig. 12.13) (12). An example of a GAMMA-I case is shown in Fig. 12.14.

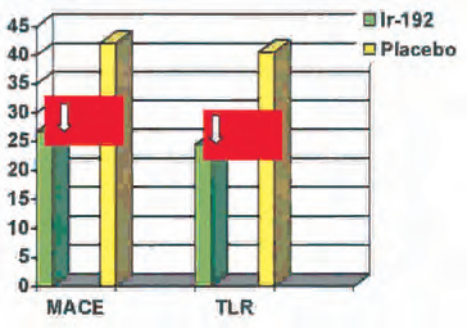
GAMMA-I was also the first study with sufficient patients to be able to demonstrate a distinct dose-response relationship. When the delivered radiation doses were normalized to a distance of 2 mm from the source, it was apparent that doses less than 8 Gy had little effect on the restenotic process, while patients who received ≥ 14 Gy (at 2 mm) derived the most benefit from the radiation therapy (an intermediate response was seen in the subgroups of patients receiving 8 - 10 Gy and 10 - 12 Gy)(13). Based on the results of this study, a FDA Advisory Panel has unanimously voted to grant pre-marketing approval to the Checkmate System for clinical use in the United States.

One unexpected late complication seen in the GAMMA-I study was a very significant 6% incidence of late (> 30 days post-procedure) stent thrombosis in the irradiated patients. When the data was from all the major studies using Ir-I92 (SCRIPPS, GAMMA-I, WRIST) was analyzed more critically, a 6 - 9% incidence of stent thrombosis was found in patients receiving radiation therapy; however, this was found to affect *only the subgroup of patients randomized to the radiation therapy arm, who also received a new stent at the time of the re-intervention* (in these studies, more than 80% of the patients received a new stent in an effort to optimize the angiographic result). These early protocols called for post-procedure antiplatelet therapy for only 4 weeks (as is standard in patients receiving new stents). Similar problems with late stent thrombosis are also being reported in trials employing beta-emitting isotopes (the Boston Scientific/SCIMED dose - finding study, Beta-WRIST, Beta-Cath, etc), indicating that late stent thrombosis is not a function of the isotope, but a result of the "interaction" between a new stent and radiation. While a number of esoteric mechanisms have been proposed to explain this high incidence of post-radiation stent thrombosis (14), the most likely explanation is that the radiation causes a delay in the reendothelialization of the new stent. This results in exposure of a highly thrombogenic bare metal to the blood stream, making these patients susceptible to late stent thrombosis, once the antiplatelet therapy is stopped. This theory has been validated by the very low incidence of late stent thrombosis seen in the SCRIPPS III and WRIST-PLUS studies (Tierstein P, Waksman R - Personal communication). These are both on-going registry studies in which all patients receive postprocedure radiation; patients who require a new stent to optimize their angiographic outcome are prescribed prolonged antiplatelet therapy (for upto 1 year). Similarly, the randomized START trial (vide infra) had *no instances* of late stent thrombosis (this

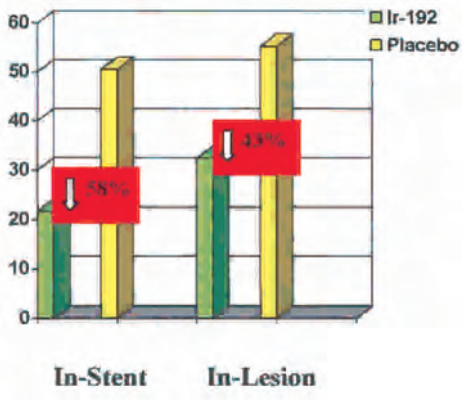
* MACE = Major Adverse Cardiac Events, comprising death, myocardial infarction, or need for TLR/CABG

may actually be a reflection of the small number of patients who actually received a new stent, rather than a function of the duration of antiplatelet therapy).

Figure 12.13 : Summary of GAMMA - I Results



GAMMA-I:
9 Months Clinical Outcomes



GAMMA-I:
6 Months Angiographic Restenosis Rates

GAMMA-I: Late Stent Thrombosis

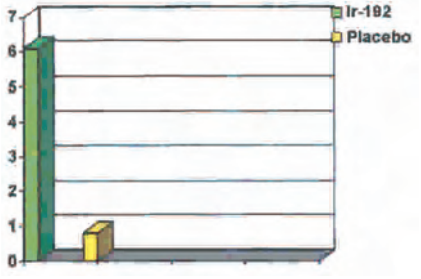


Figure 12.14: Example of a GAMMA-l Case

Figure 12.14a: In-stent Restenosis in a Rt. Coronary Artery

Figure 12.14b: Post-intervention

Figure 12.14c: Radiation Source Ribbon in Place

Figure 12.14d: 6 Month FoUow-up Angiogram

The Washington Hospital Center has developed a variant of this approach, wherein the dose is prescribed at a standard distance of 2 mm from the source center - the **WRIST** (**W**ashington **R**adiation for **I**n-Stent Restenosis **T**rial) Study. One hundred and thirty patients with in-stent restenosis in native coronaries or vein grafts were randomized to a post-intervention placebo or 15 Gy prescribed at 2 mm from the source, using a similar Ir-I92 seed train. Lesions up to 47 mm in length were treated. A cross-over was allowed from the placebo to the radiation-arm, if the placebo treated patient failed. At 6 month clinical and angiographic follow-up, the TLR was reduced by 79%, TVR by 61 %, the combined event endpoint (MACE) by 63% (Fig. 12.15) and angiographic restenosis by 67% - Fig. 12.16 (15). These results are remarkably consistent with the SCRIPPS and GAMMA-I data, hinting that, in vessels within this diameter range, a fixed dose prescription point may be practical and IVUS may not be mandatory in all patients.

The **GAMMA-II** Study was designed to test the **WRIST** concept in a multi-institutional setting. It was a registry study (all patients got radiation) in a group of patients similar to the **GAMMA-I** population. The device used was also identical, but a dose of 14 Gy was prescribed at a distance of 2 mm from the source axis (similar to the WRIST study, and in keeping with the AAPM TG 60 recommendations). IVUS was performed for prospective, post-procedure, dosimetric evaluation and failure analysis, but was not used for dose prescription. The target of 120 patients was rapidly accrued. Though the study had a higher proportion of patients with calcific lesions (31 % V s 10% for the placebo group of GAMMA-I), the results were remarkably consistent with those from the SCRIPPS, WRIST and GAMMA-I studies (Fig.12.17).

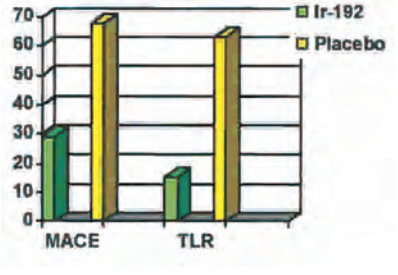


Figure 12.15 :WRIST-
6 Months Clinical F-U

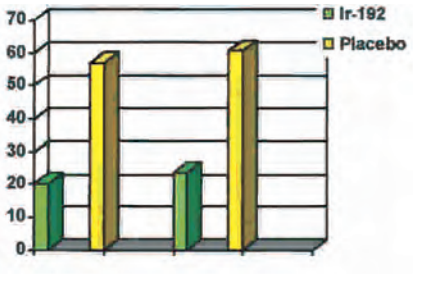
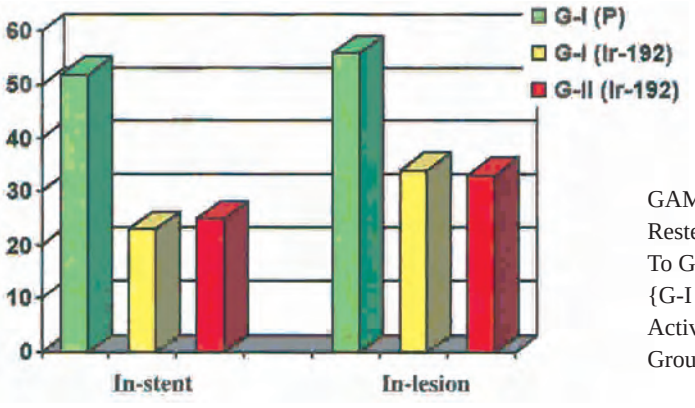
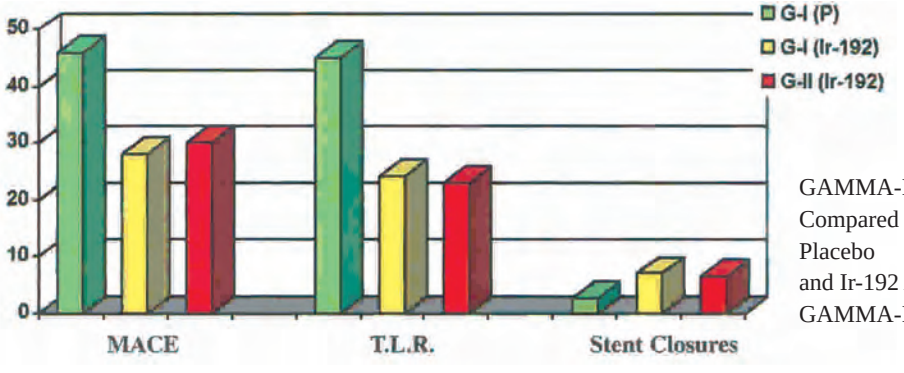


Figure 12.16 : WRIST-
6 MonthsAngiographic Restenosis Rates



GAMMA-II {G-II (Ir-192} Restenosis Rates Compared To GAMMA-I Placebo {G-I (PH) and GAMMA-I Active{G-I (Ir-192} Groups.



GAMMA-II Results Compared To Placebo and Ir-192 Arms of GAMMA-I

Figure 12.17: Summary of GAMMA-II Results

The **LONG-WRIST** study (reported at the ACC Meeting, March, 2000) enrolled 120 patients in a 2 center, double-blinded, placebo controlled randomized trial. Inclusion criteria included a *lesion length of 36 - 80 mm and a vessel diameter of 3 - 5 mm.* 14 - 15 Gy was prescribed at 2 mm from the source in patients with vessel diameters of 3 - 4.0 mm, and 15 Gy was prescribed at 2.4 mm from the source in patients with a vessel diameter of > 4 mm. This was a very high risk population with 50% having had a prior myocardial infarction, 40% having undergone a previous bypass surgery and 50% having in-stent restenosis. Mean lesion length was 31 mm and the reference vessel diameter (as analyzed by the angiographic core laboratory) was smaller than expected - 2.5 mm - in both arms. As part of the interventional procedure, about 66% patients had a rotational atherectomy and 20% had laser ablation. In the Ir-192 arm, 71.7% patients had new stents implanted, while the corresponding figure was 58.3% in the placebo arm. Mean dwell time was 21.8 minutes, with a maximal luminal surface dose of 45 Gy. A cross-over was allowed in the study design, and 29 of the 60 patients randomized to the placebo arm did indeed cross-over. The 6 month angiographic result showed an in-stent restenosis rate of 32% in the irradiated patients Vs 71 % in the placebo group ($p = 0.0002$); equivalent figures for in-lesion restenosis were 46% and 78% respectively ($p = 0.001$). There was a reported "edge effect" of 13% in the irradiated group Vs 6.6% in the placebo patients (p = NS). IVUS analysis confirmed that the benefit from radiation therapy was related to the brachytherapy-induced reduction in neointimal proliferation. When MACE was looked at as a composite endpoint, there was a statistically significant reduction in the irradiated patients, 38.3% Vs 61.7% in controls (p =

0.01). However, there was a fairly high incidence of late stent thrombosis in the radiation cohort (total occlusion rate of 15% in the Ir-192 arm Vs 6.7% in the placebo patients). This was once again related to the placement of new stents at the time of brachytherapy, in conjunction with an inadequate duration of antiplatelet coverage.

Other studies employing the Ir-192 seed train include the **SCRIPPS - II,** which is studying more diffuse lesions (upto 65 mm, 100 patients), **SCRIPPS - III** (registry study evaluating the efficacy of prolonged antiplatelet therapy in preventing late stent thrombosis), **SVG WRIST** (randomized study of radiation Vs placebo in patients with in-stent restenosis in saphenous vein grafts), **WRIST-PLUS** (registry study of 120 patients studying the efficacy of 6 months antiplatelet therapy in preventing late stent thrombosis), **High Dose WRIST** (registry of 60 patients with Long WRIST-like patients and vessels upto 4 mm diameter, dose 15 Gy at 2.4 mm from the source), **GRANITE** (**G**amma **R**adiation to **A**theromatous **N**eointima using **I**ntracoronary **T**herapy in **E**urope) is an European registry study of patients with native artery in-stent restenosis employing a newer Cordis hand-cranked delivery device), and **INDIRA** (a randomized study in India, studying the effect of post-PTCA radiation in de novo lesions employing a catheter designed by Cook Inc., and an Ir-192 seed train manufactured by Alpha-Omega Inc.).

The Novoste Sr/Y-90 Intravascular Radiation System

This system (Fig. 12.18) consists of three basic components - a) The Novoste™ Beta-Cath™ radiation delivery catheter, which is an over the wire type of intracoronary catheter designed to be used after a successful interventional procedure (Fig 12.20); b) The beta-radiation emitting Sr/Y-90 Seed Train (Fig. 12.19); which, in turn, is driven by the c) "Hand-held Transfer Device", which is quite akin to the balloon inflation syringe used for angioplasty (Fig 12.21).

The BetaCath delivery catheter has the following features:

- ≤ 7 Fr (0.078") guide catheter compatible
- ≤ 0.014" guidewire compatible
- Two radiopaque markers measuring 35, 45, and 65 mm apart to designate the 30 mm, 40 mm, and 60 mm treatment zones respectively
- A tapered tip from 5 Fr to 2 Fr distal to the distal radiopaque marker
- An open guidewire lumen allows the catheter to travel over a 300 cm guidewire

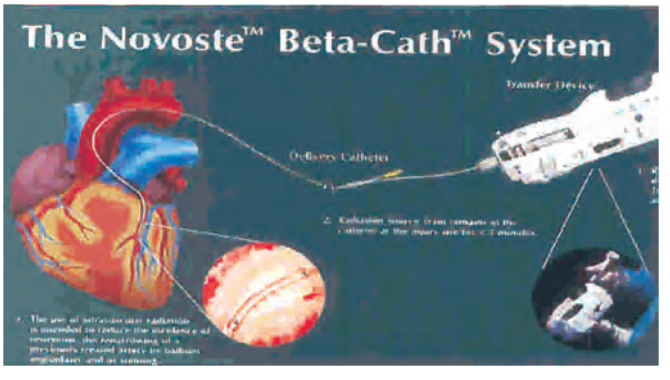


Figure 12.18 : The Novoste BetaCath System. Courtesy Novoste Corporation

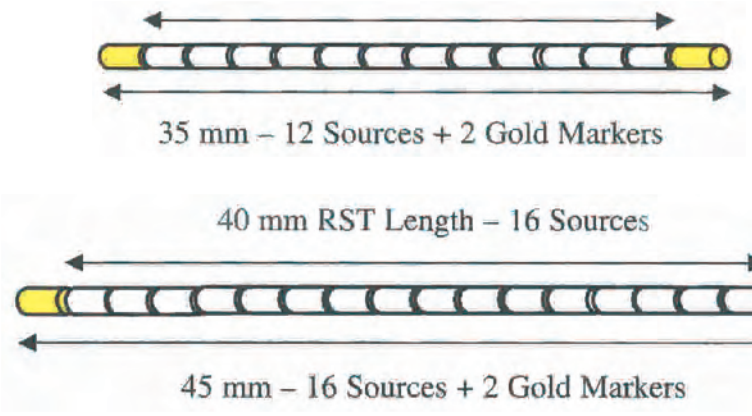


Figure 12.19 : The Sr/Y-90 source trains. Courtesy Novoste Corporation

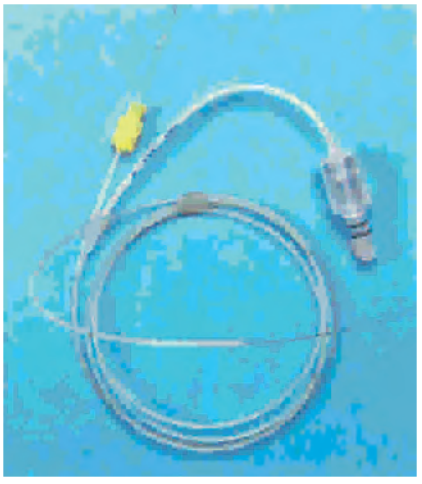


Figure 12.20: The BetaCath monorail catheter. Courtesy Novoste Corporation

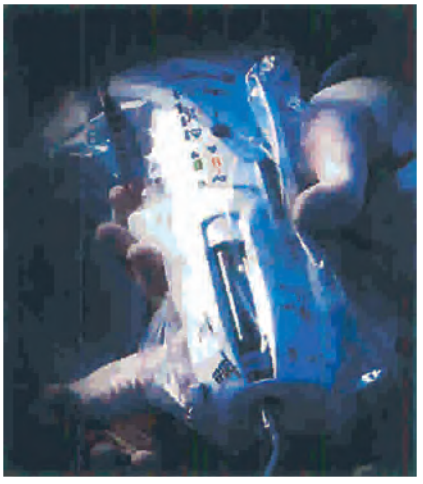


Figure 12.21 : The Novoste Handheld Transfer Device. Courtesy Novoste Corporation

- A second dedicated lumen contains the source train
- A third lumen completes the fluid path (fluid return lumen)
- A proximal depth marker positioned approximately 90 cm from the distal tip that facilitates placement of the delivery catheter through the femoral route
- A proximal end consisting of a connector that employs squeeze tabs to ensure a secure connection between the delivery catheter and the transfer device
- Working length of 135 cm

The active source train consists of a "train" of 12 (30 mm source train) 16 (40 mm source train) or 24 (60 source train) miniature cylindrical radioactive sealed sources containing Strontium/Yttrium-90, and two (one proximal and one distal) gold colored radiopaque markers. The principal radiation emission is beta particles with a maximum energy of 2.27 MeV. The source has a half-life of 28.8 years.

Following a successful intervention, the PTCA catheter is withdrawn, the Beta-Cath™ catheter is threaded over the guidewire and positioned across the site of angioplasty "injury" with the transfer device connected to the Beta-Cath. A disposable syringe filled with sterile water "powers" the transfer device which employs an ingenious system of hydraulics to deliver the source train to the catheter tip within a few seconds. The transfer device serves to transport, hold and deliver the source train, while shielding the operator from the beta radiation. Though there is no active attempt at centering, it is presumed that the pulsatile blood flow within the coronary artery, the cardiac contractions and the size & flexibility of the catheter result in passive centering of the source during dose delivery. For withdrawal of the sources back into the transfer device, the operator reverses a switch on the transfer device; this reverses the path of fluid within the catheter, such that continued injection of fluid into the catheter results in a return of the sources into the transfer device. The average treatment time is about 3 - 4 minutes and the beta source allows all treating personnel to stay with the patient during the therapy. The physician has complete control over the radiation source at all times during the treatment, while the Beta-Cath™ provides excellent tactile feedback to the operator throughout the procedure.

This device was first used in a Phase I study at the Emory University and Rhode Island Hospital. 20 patients were enrolled in this **BERT** (Beta Energy Restenosis Trial) study and were treated with doses of 12 Gy, 14 Gy or 16 Gy (prescribed at 2 mm from the center of the source), and a further cohort of patients were enrolled in a supplemental study in Canada. The enrollment criteria included vessels ranging from 2.5 - 3.5 mm in diameter, with a lesion that could be dilated by a single 20 mm balloon. The source dwell times ranged from 2.2 - 3.4 minutes. There was no attempt made to center the source. Since this was not a randomized trial, it is difficult to comment on efficacy. However, at a 6 month follow-up, the angiographic findings showed a very encouraging reduction in the percent diameter restenosis. The cumulative frequency distribution of MLDs showed a very close apposition of the post-PTCA and the follow-up curves, indicating a very low late loss index ("freezing of the post-angioplasty result"). When compared to a matched historical control group, the differences were quite significant (16). The **Canadian arm of the BERT** study enrolled another 30 patients, and the **European arm (BERT 1.5)** treated 30 more patients to tota l86 patient enrollment. The reported restenosis rate for this entire cohort was 17% with a 9% late loss index (though 6 additional patients required revascularization for edge failures).

BRIE (**B**eta **R**adiation **I**n **E**urope) is a registry trial in Europe (20 sites) which enrolled 150 patients. The unique feature of this study was that it allowed for treatment of lesions in up to two vessels in the same session. Interim results revealed a target vessel revascularization rate of about 30% with a late loss index for the entire cohort of about 13%. Some of these results could be accounted by the problems in the conduct of the trial - thus, patients with long lesions and diffuse disease were included (with a higher proportion of procedural complications), the interventional results were not always optimal (residual stenosis of > 50% in a number of patients), antiplatelet therapy was used for a very short time in this cohort (60% of whom had a new stent), the core laboratory-identified incidence of geographic miss was very high (almost 50%) and finally, at follow-up, some patients got a TVR despite "a core-laboratory estimated < 50% stenosis". This study highlights the importance of both, a meticulous interventional technique as well as close attention to the details of radiation therapy delivery, in achieving optimal results.

RENO (**E**uropean surveillance **R**egistry with the **No**voste Beta-Cath System) is a prospective, multi-national (50 sites) surveillance registry designed to study the Novoste Beta-Cath system in patients with native arterial disease or bypass graft stenosis. Treatment of up to three vessels is allowed.

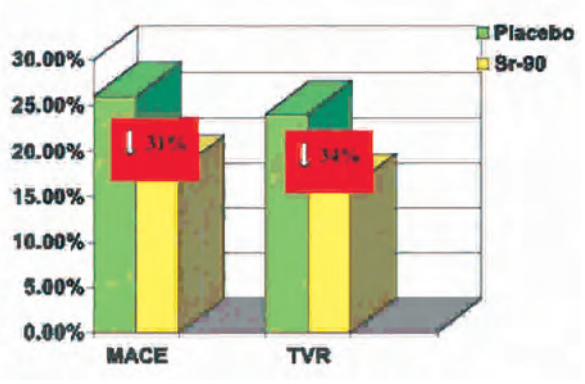
The **Beta-Cath** trial is now underway as a double-blinded randomized study in more than 50 US and European centers. Patients with de novo stenotic lesions that can be treated by a balloon ≤ 20 mm in length are eligible. Following PTCA, patients are stratified into two groups - those with a successful PTCA outcome (< 30% residual stenosis) remain in the "PTCA alone" arm and are randomized to radiation therapy or placebo treatment; patients with suboptimal angioplasty results (significant residual stenosis, mild dissections) are stratified to the "stent-rescue" arm, and are similarly randomized to radiation therapy or placebo, *to be followed by stenting* to optimize the interventional result. A radiation dose of 14 or 18 Gy is prescribed at a distance of 2 mm from the source depending on reference vessel diameter (≥ 2.7 - ≤ 3.3 mm, and > 3.3 - ≤ 4.0 mm respectively). The planned accrual of over > 1500 patients is complete, and the follow-up is underway. *This is the largest trial of intracoronary brachytherapy and will serve as a pivotal study to assess the role of post-angioplasty radiation in de novo, non-stented and stented lesions.*

The **START** (**ST**ents **A**nd **R**adiation **T**rial) study is a multi-center randomized protocol using the Novoste device in patients with in-stent restenosis. 476 patients were accrued from 50 sites in the US and Europe. Due to the concerns of shielding of the beta particles by the pre-existing stent struts (estimated to be about 10%), the prescription dose was increased to 16 and 20 Gy at a distance of 2 mm form the source (for reference vessel diameter ≥ 2.7 - ≤ 3.3 mm, and> 3.3 - ≤ 4.0 mm respectively). At the initiation of the protocol, antiplatelet therapy was used for only 1 month; subsequently this was modified and the latter cohort of patients received 3 months of antiplatelet therapy. New stents were deployed in only about 20% of the total patient population. While none of the patients presented with clinical stent thrombosis, follow-up angiograms performed at 8 months revealed angiographic total occlusions in about 4% of cases in both the placebo and the irradiated arms. The results can be summarized as follows (Fig. 12.22)(17):

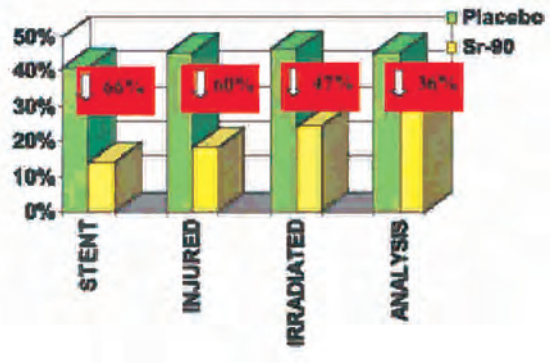
- No late clinical thrombosis in patients undergoing radiotherapy 0-240 days
- 31 % reduction in MACE (p = 0.039) - Defined as death, MI, and TVR
- 42% reduction in TLR (p = 0.008)
- 34% reduction in TVR (p = 0.026)

Angiographic core laboratory analysis revealed a fairly high (> 30%) incidence of geographic miss. Though the presence of a geographic miss did not seem to predict for a treatment failure in this study, the precise relationship between a geographic miss and "edge failures' will need to be clarified. Based on the results of this study, a FDA Advisory Panel has unanimously voted to grant pre-marketing approval to the Novoste System for clinical use in the United States.

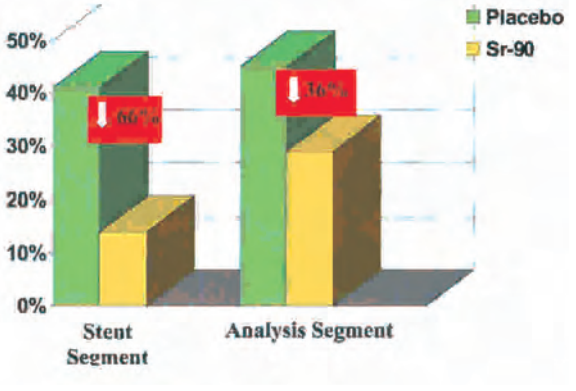
Given the relatively "short" (30 mm) source train, there were some initial concerns about the efficacy of the system in longer lesions. A subgroup analysis of the START data showed that use of the Novoste BetaCath device was as effective (if not more so) in lesions longer than 15 mm (Fig. 12.23).



8 MONTH CLINICAL OUTCOMES



8 MONTH RESTENOSIS RATES BY SEGMENT

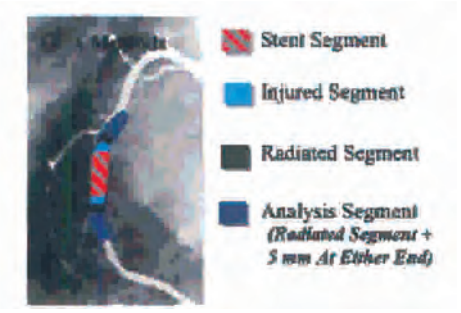


8 MONTH ANGIOGRAPIDC OUTCOME

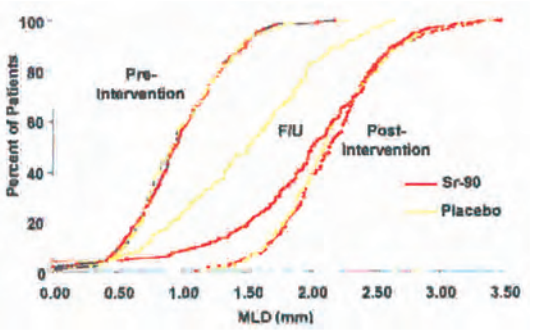
Figure 12.22 : Summary of START Results

Yttrium-90 Wire Boston Scientific/SCIMED Intravascular Radiation System

This device consists of a flexible titanium coated radioactive yttrium-90 coil (outer diameter 0.014", length 29 mm, max energy =2.284 MeV, half-life 64.1 hours, max activity 150 mCi) mounted at the end of a 0.014" delivery wire (Fig. 12.24). This source is centered by a 25 mm long, segmented balloon (3.4 Fr), consisting of four interconnected compartments, which is



QCA Methodology To Define Restenosis Rates



Cumulative Frequency Distribution Of Stent Segment MLD Showing Separation Of The Placebo & Sr-90 Curves At Follow-up As An Indicator Of Treatment Efficacy

mounted on a monorail double lumen catheter shaft (Fig. 12.25). Good trackability of the centering balloon and high flexibility of the yttrium-90 coiled source facilitate use of the system even in a very tortuous coronary anatomy. To minimize the attenuation of the beta-radiation, the balloon is inflated with carbon dioxide. A computerized afterloader (Fig. 12.26) is employed to deliver the source and regulate the dwell times. Because the centering balloon occludes the flow in the coronary artery, the treatment can be briefly interrupted if the occlusion is not tolerated - the computerized afterloader makes this fractionation of dwell times especially convenient. The afterloader also has additional safety features like an automated computation for daily source decay, numerous fail-safe mechanisms and the provision for a dummy wire run to ensure patency of the path as well as allow for precise positioning of the balloon before the active source is deployed. The use of a beta source allows the procedure to be done with the radioprotection conditions of a conventional catheterization laboratory. The beta-emitting yttrium source is good for about a week; thereafter, the activity decays to a point where treatment times are too prolonged. In practice, in the clinical trials, a new source is shipped to the sites every Monday for use from Tuesday to Friday.

Urban et al reported the results of an **initial pilot study** (18). Following a successful PTCA, 18 Gy. was delivered to the inner arterial surface (i.e. to the surface of the balloon) with dwell times of 2.5 min. to 10 min. without any problems. 15 patients were treated with this approach. There were no complications that could be attributed to the radiation therapy. However, with a mean follow-up of 6 months, 4/15 patients required target lesion revascularization and 6/15

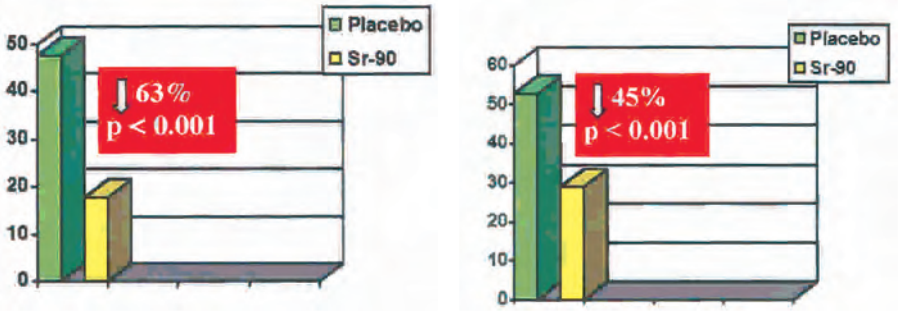


Figure 12.23: START Angiographic Restenosis Rates For Lesions > 15 mm (Mean 21.8 + 5.3 mm)

patients showed evidence of angiographic restenosis. A possible explanation for these negative results lies in the dosimetry of the protocol. The authors designed their clinical dose prescription based on experience with rabbit carotid and iliac arteries, both of which are considerably thinner < 0.4 mm) than atherosclerotic human coronaries. Consequently, a luminal dose of 18 Gy, which was effective in rabbits, resulted in only 8 Gy at 1 mm and less than 4 Gy at a depth of 2 mm into the arterial wall. There is also the theoretical concern that the centering balloon may have caused hypoxia in the adjoining arterial wall, something that could have further decreased the biological effectiveness of the radiation.

A subsequent **dose finding protocol** was completed at 5 European centers (19). 180 patients were enrolled. Doses of 9, 12, 15 and 18 Gy were delivered at 1 mm into the vessel wall, employing the computerized after-loading system. It is important to note that the reference vessel diameter (and not the MLD) was used to size the centering balloon; this could potentially result in some degree of "overdilatation" of the target segment with "thinning out" of the vessel wall in this segment - issues that are important from the dosimetry view point, especially when attempting to

Figure 12.24 : Delivery Wire With Source Coil (From Verin V, Popowski Y. Clinical Trials Using Beta Energy Radiation: Experimental and Clinical Experience with Schneider-Sauerwein Intravascular Radiation System. In: Waksman R. ed. Vascular Brachytherapy, 2nd Ed. 1999. Armonk, NY: Futura Publishing Company, with permission)

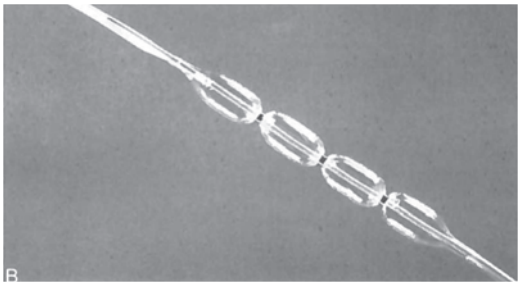
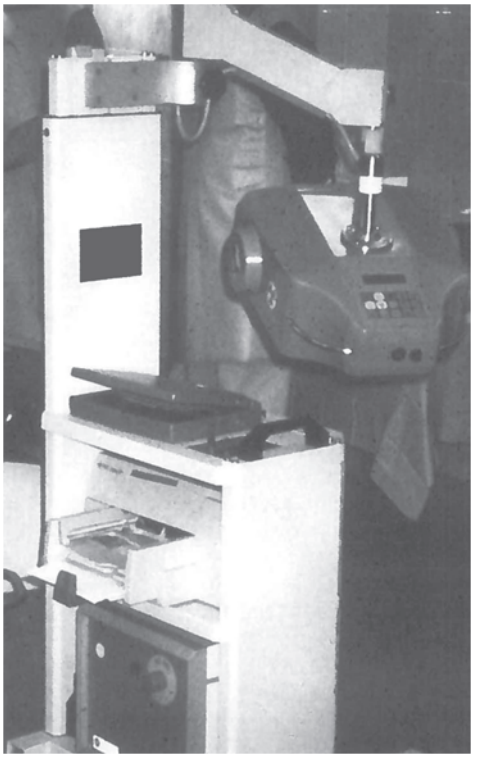


Figure 12.25 : Centering Catheter. (From Verin V, Popowski Y. Clinical Trials Using Beta Energy Radiation:Experimental and Clinical Experience with SchneiderSauerwein Intravascular Radiation System. In: Waksman R. ed. Vascular Brachytherapy, 2nd Ed. 1999. Armonk, NY: Futura Publishing Company, with permission)

Figure 12.26 : Afterloader. (From Verin V, Popowski Y. Clinical Trials Using Beta Energy Radiation: Experimental and Clinical Experience with Schneider Sauerwein Intravascular Radiation System. In: Waksman R. ed. Vascular Brachytherapy, 2nd Ed. 1999. Armonk, NY: Futura Publishing Company, with permission)



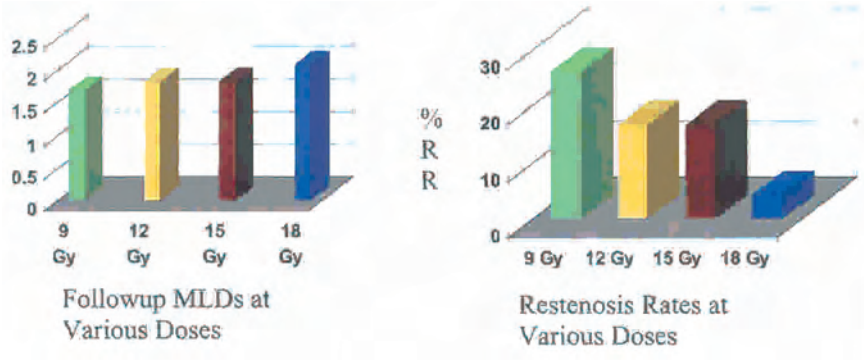


Figure 12.27: Summary of the "dose-finding" protocol

compare this data with that from other studies. 45 patients were treated at each dose level, and there was no control group. The preliminary results are quite encouraging (Fig. 12.27) :

When patients were divided into those that were treated with balloon angioplasty alone and those that received a stent, it was apparent that the balloon angioplasty patients showed a distinct dose-response with a statistically significant difference in restenosis rates and follow-up MLDs between the 9 Gy and the 18 Gy arms; this dose-response relationship was much less impressive in the stented patients. Also, the patients who received a new stent experienced a fairly high rate of total occlusion (? stent thrombosis) - 4/38 patients (10.5%) patients had a total occlusion over the follow-up period.

The **Beta-WRIST** (20) is another feasibility study completed at the Washington Hospital Center using the same device. 50 patients with in-stent restenosis were treated. A dose of 20.6 Gy was prescribed at 1.2 mm. There was a similar late thrombosis rate of 10%; however, the 6 month angiographic restenosis rate was only 22%; when compared to the historical control of the WRIST study (vide supra), this represented a > 50% reduction in the need for target lesion or target vessel revascularization. A multi-institutional, randomized study using this device, is planned to begin in the United States later this year.

The Galileo ™ Coronary Source Wire System

(The Guidant Corporation, Vascular Intervention, Houston TX, USA)

This system consists of a source wire (Fig. 12.28) containing up to 300 mCi of P-32 (a 0.018" Nitinol wire with a 27 mm P-32 source hermetically sealed at its distal tip), a rapid exchange type 3.9 Fr centering catheter with a 27 mm long spiral balloon (to allow for antegrade perfusion during the treatment - Figs. 12.29, 12.30) and a computer-controlled automatic remote afterloader which houses the source, allows for computer-aided dosimetry, and delivers/retracts the source (Fig 12.31). The computer-controlled afterloader allows for easy dose fractionation. There is also the provision for an inactive dummy wire run to check the "patency" of the entire pathway before the active source is sent out. Other safety features that are built into the system include a force sensing mechanism that prevents any attempts to advance the wire in the face of a significant resistance in the pathway, and an emergency stop button with a backup motor and a manual source wire retraction mechanism. The design is being modified to allow for a stepping source system for maximal flexibility in treating various lesion lengths.

PREVENT (**P**roliferation **RE**duction with **V**ascular **EN**ergy **T**rial) was a feasibility study using this device at 3 centers in the United States. 72 patients were randomized to receive 0 Gy (control) or 16,20 or 24 Gy at 1mm in the vessel wall. 65% were de novo lesions and 35% were restenotic, including 29% in-stent restenosis. Follow-up angiography at 6 months showed a Late Loss Index of only 5% in the irradiated patients Vs 51 % in the controls ($p = 0.0001$). Similarly, the restenosis within the treated segment was reduced from 33% in the control group to 6% in the irradiated patients ($p = 0.015$). Unfortunately, there were a significant number of patients in the irradiated group who developed restenosis at the margins of the treated segments, so that the incidence of composite MACE was 16% in the irradiated patients Vs 24% in the controls. No differences were seen between the patients who received stents Vs those who were treated with balloon angioplasty alone. There was also no evidence of a dose-response relationship across the doses studied. This study was supplemented by the PREVENT-CE trial, which is a similar feasibility study at 5 sites in Europe. **INHIBIT** (**IN**timal **H**yperplasia **I**nhibition with **B**eta **I**n-stent **T**rial) is a currently active multi-institutional, randomized, double-blinded trial looking to accrue 310 patients with in-stent restenosis. Patients are being randomized to a placebo control arm V s 20 Gy prescribed 1 mm into the arterial wall using this device (21). **DURABLE** (**DU**tch **RA**ndomized **B**rachytherapy study for **L**ong-term evaluation of **E**fficacy) is a randomized, placebo-controlled, double blinded study employing this device in patients with up to two vessel disease. 900 patients are scheduled to be enrolled at 9 centers in the Netherlands.

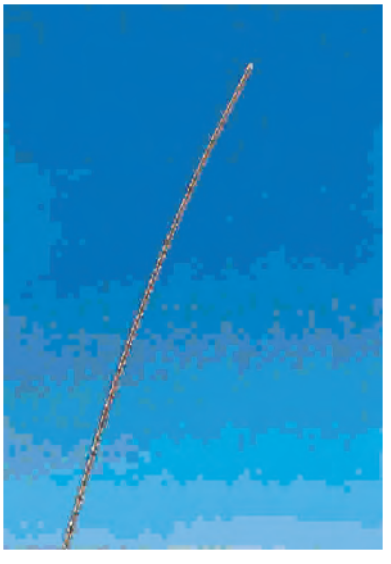


Figure 12.28: P-32 Radioactive source "wire". Courtesy: Guidant Corporation

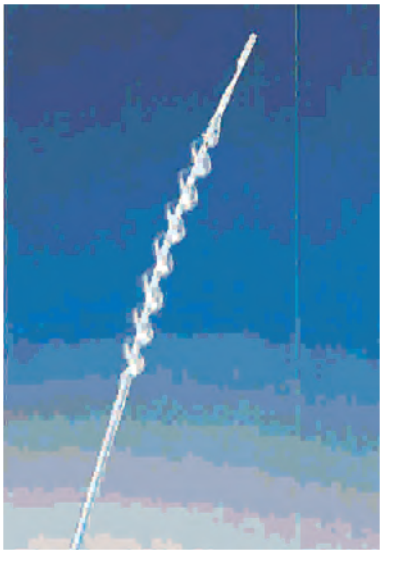


Figure 12.29 : Close-up view of the Guidant spiral balloon catheter. Courtesy : Guidant Corporation.

The Angiorad Mechanically After-loaded Iridium-192 Wire System

This system is composed of three components: a small flexible source wire, a delivery catheter and a mechanical (manually operated) after-loader to advance and retract the source. The source wire is a 0.0014" nitinol tube with a 3 cm core of Ir-192 (500 mCi) at its tip. The source is entirely encapsulated, and the wire is flexible enough to allow access to all locations in the coronary vasculature. The delivery catheter is a 3.5 Fr catheter with a 1 cm monorail tip, and a 3 cm centering balloon just proximal to the monorail. The after-loader is a small portable unit,

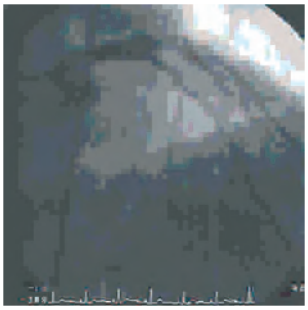


Figure 12.30: A PREVENT case showing the spiral catheter and its ability to allow antegrade perfusion. Courtesy: Guidant Corporation

Figure 12.31: The Galileo remote afterloader. Courtesy : Guidant Corporation

which includes a high-density tungsten safe to house the source wire, a wire spool and manual crank to advance/retract the wire with a clutch device to regulate the wire motion. The pilot phase of **ARTISTIC** (**A**ngiorad **R**adiation **T**echnology for **I**n-**S**tent restenosis **T**rial **I**n native **C**oronaries) study accrued 26 patients with in-stent restenosis who were treated to 12, 15 or 18 Gy prescribed at 2 mm from the source. Six month angiographic follow-up showed a binary stenosis rate of only 10% with a late loss index of only 0.12%. However, the pilot phase of **ARREST** (**A**ngiorad **R**adiation for **RE**stenosis **T**rial), which used this device in 25 non-stented de novo or restenotic patients, had an angiographic restenosis rate of 45% (22) - this could probably be explained by the relatively low dose (< 8 Gy) delivered to the adventitia, as estimated by the IVUS that was used for dose-prescription. **SMARTS** (**SM**all **A**rtery **R**adiation **T**herapy **S**tudy) is another study that is planned to test one of the claimed strengths of this system, i.e. the ability of the flexible source wire to negotiate small/tortuous vessels. Patients with de novo lesions in small vessels < 2.75 mm in diameter will be enrolled in this study.

Summary

Several different endovascular brachytherapy systems are currently being evaluated. The catheter-based systems are the only ones with a significant clinical experience. Amongst these, the manually afterloaded systems offer the advantage of simplicity of operation, with an excellent tactile feedback. Remote afterloaders offer the benefits of computer-controlled source delivery and withdrawal, automated dwell time calculations, and the potential for "stepping" the source to further optimize the treatment delivery (especially in challenging situations like bifurcation stenosis, tandem lesions, etc.). These benefits, however, come at the expense of a fairly sophisticated system with the potential for electronic and mechanical malfunctions. As regards the different isotopes, the early data indicates that both gamma- and beta-emitters "work". This implies that purported advantages and disadvantages of various isotopes may be, to some extent, theoretical; what is probably most important is appropriate patient selection and meticulous attention to the details of protocol implementation.

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13

Clinical Approaches To Vascular Radiotherapy - The Peripheral Vessels

Paralleling the evolution of vascular interventions, some of the earliest applications of endovascular brachytherapy were in the peripheral arteries. As a historical footnote, it is remarkable that Brasfield and Henschke first employed the "endovascular" approach for brachytherapy in 1958; they used an afterloading technique in which a catheter loaded with radioactive sources was introduced into the internal mammary artery to irradiate internal mammary lymph nodes in the management of breast cancer. (1). Later, in 1990, Androsov et al reported a remote-controlled afterloading technique, using the Nucletron micro-Selectron™ (Nucletron Corporation, Columbia, MD) LDR/MDR afterloader, to achieve the same purpose (2). However, it was only in 1994 that Liermann and Bottcher first described the feasibility of using endovascular brachytherapy (EVBT) to actually inhibit post-angioplasty restenosis in the femoro-popliteal setting (3). This chapter will review the use of radiation therapy to prevent post-angioplasty restenosis in the peripheral vasculature.

External Beam Radiotherapy Studies

Since the majority of the early animal work was conducted by interventional cardiologists, the initial experiments employed an endovascular approach. The consistently favorable results from these laboratory experiments acted as the driving force behind the development of several innovative approaches for delivery of endovascular brachytherapy. However, because of its the noninvasive nature and the potential for wide-spread applicability, external beam radiotherapy has always remained an attractive option. External beam radiotherapy has several biological, physical, logistic and patient related advantages (4):

- Patient Related Advantages:
  - i) Blood flow is not compromised by an intra-luminal device; this is especially important in the immediate peri-procedural period when the intervened vessel is prone to spasm and thrombosis.
  - ii) Avoids "prolongation" of the interventional procedure.
  - iii) No need to transport the patient from the Interventional Suite to the Radiation Oncology Department with catheters, etc. in place; this can be a significant issue when the radiology suite and the radiation oncology departments are far apart and especially when they are on different campuses. Further, several interventional radiology departments do not have an on-site radiation oncology department; this can severely limit the widespread applicability of this technology.

- Biological Advantages: The radiation biology of fractionated external beam radiation therapy is well established. On the other hand, there is really very little experience with wide-spread use of single, large fraction radiotherapy in non-palliative settings. The only curative use of single, large fractions of radiation therapy is in the treatment of arterio-venous malformations, and even here doses are usually in the order of 15 - 20 Gy. This should be contrasted with the 45 - 70 Gy that is delivered as a single dose to the arterial intima with endovascular brachytherapy.

  i) External beam radiotherapy is delivered at a constant and fixed dose rate. This may be of some clinical importance, especially when one considers that the treatment times with isotopes like Ir-192 already approach the repair half-times of the target smooth muscle cells. Any further prolongation of treatment times, due to source decay over the clinically useful life of the isotope, can potentially decrease the biological efficacy of the same nominal dose of radiation, unless this is accounted for. (5)

  ii) External radiation therapy allows for the possibility of dose-fractionation with the potential for dose-escalation. The early work with endovascular radiotherapy has implied that there may be a fairly large therapeutic window of dose that one could safely exploit. However, with the increasing awareness of complications like late stent thrombosis, it is more than likely that "there may be no free lunch". At any level of late radiation effects, fractionation of the radiation dose would always allow for dose escalation, thus improving the therapeutic ratio.

  iii) Radiation delivery can be "synchronized" with the proliferation kinetics. Ionizing radiation is most effective against proliferating cells. Smooth muscle cells, in their normal state, are resting and quiescent; it is the PTCA injury that converts them into proliferating cells. This conversion takes place under the influence of several intermediary cytokine cascades, and follows a distinct temporal profile (6). On purely theoretical grounds, post-angioplasty radiation may be more effective (or a smaller dose may be adequate) if it is delivered 24- 72 hours after the angioplasty "stimulus".

  iv) Potential for use of radiosensitizers or radioprotectors. Both these classes of agents have the ability to markedly improve the therapeutic ratio; however, both of them are most effective in the setting of a proliferating cell population, and may work best at a later time from the angioplasty injury.

- Advantages from a physics viewpoint:

  i) External beam radiotherapy offers the most precise and well established dosimetry; this is in marked contrast to the paucity of data with brachytherapy sources at millimeter distances (especially with beta-emitting isotopes).

  ii) There is no need to constantly account for source decay, an important issue with short halflife isotopes.

  iii) No radiation safety concerns related to source storage or transportation.

  iv) By its very nature, endovascular brachytherapy is associated with a fairly steep dose gradient across the vessel wall. Unfortunately, the radiation target - the smooth muscle cell- lies further away from the source, while the dose-limiting structure - the endothelium lies in close proximity to the source (this has been rather picturesquely compared to treating prostate cancer with a radiation source in the rectum !). External

beam radiotherapy would, of course, provide a homogeneous dose across the entire vessel wall.

v) Since the radiation is delivered from "outside", there is no need for complex or potentially flow-compromising centering devices.

vi) The dose delivery is also not affected by eccentric plaques, plaque composition or metallic stents - issues that are especially important with beta-emitters.

- Logistical Advantages:

i) Since the therapy is performed in the Radiation Oncology department, there are no radiation protection problems.

ii) Vascular interventions may need to be performed on a semi-emergent basis. Use of external radiation therapy would allow this technology to be easily integrated into the normal working routine of the interventional laboratory and the radiation oncology department. This, in tum, would address the big issue of manpower and scheduling conflicts.

However, due to some technical problems with this approach (Table 1), it has been investigated in the femoropopliteal region in only one small German study by Steidle et al (7). They reported on 24 patients treated with postangioplasty and stenting; 11 of these received postangioplasty 12.5 Gy external beam radiation in 2.5 Gy daily fractions. At a follow-up interval approaching 1 year, only 2 out of the 11 irradiated patients required re-intervention, while 8 of the 13 "controls" developed restenosis.

Table 1

Technical Problems With External Beam Radiotherapy

- Additional procedures required for simulation and planning
- The target vessel lies at a varying depth from the skin along its length
- Target vessel has a complex course in the antero-posterior plane along its length
- Each patient needs a customized plan, based on a treatment planning CT scan
- Treatment delivery is technically challenging and complex, with multiple beams with custom shielding
- Verification and quality assurance can be difficult
- A higher integral dose is delivered to the patient. Because of this, the single fraction dose that can be safely delivered is less than what one can potentially deliver via an endovascular approach

The RVIPG has initiated a dose-escalation study employing external beam radiation therapy using a custom plan for each patient (Rubin P, Personal communication). This study is still under accrual (Benefit of Irradiation following Peripheral Arterial Bypass (BIPASS) Study).

Endovascular Brachytherapy Using A High DoseRate Remote Afterloader

This is the approach that has been most widely used. The Frankfurt group (8) first reported this technique in the restenotic superficial femoral artery lesions. Following a successful PTA

and stenting, the patient was anticoagulated and a 9 Fr. straight catheter was introduced through a 9 Fr. femoral introducer sheath, over a guidewire, until its tip was positioned distal to the segment to be treated. The 9Fr. catheter had a tapered tip so that a coaxially introduced 5 Fr. end-occluded catheter could not advance beyond the tip. The coaxial assembly was positioned so that its distal end marked the lower end of the irradiation field (which extended 1 cm. beyond the actual stent). The target volume was determined using a calibrated dummy source, and a treatment plan designed. The dummy source was withdrawn and the patient connected to the HDR (high doesrate) unit for treatment. A standard 10 Ci. iridium source was used and 12 Gy. was prescribed to a distance of 3 mm from the source. Because of the eccentric lie of the catheter in the vessel (due to an eccentric plaque), the calculated dose to various sectors of the vessel wall varied from 8 - 28 Gy, though the minimal and maximal dose areas were quite small (< 1.5 mm). Dosimetry for the iridium source showed that for a prescribed dose of 12 Gy at 3 mm from the source, doses of 8.77 Gy, 5.51 Gy, 3.96 Gy, and 3.03 Gy were delivered at a distance of 4 mm, 6 mm, 8 mm and 10 mm respectively. One of the major problems with this approach is that it cannot be done in the normal interventional laboratory as special shielding is needed when dealing with such high activity sources.

The procedure usually took about 200 seconds. Heparin was continued for 72 hrs., and subsequently, the patients were anticoagulated orally for 6 months. Thirty patients with 31 lesions were treated according to this protocol with a follow-up extending from 7 - 84 months, median 32.9 months. The treated length ranged from 5 to 16 cm. Follow-up CT/MR imaging did not show any adverse reactions in the perivascular tissues. Of the 28 pts. available for follow-up, 3 had restenosis in the treated segment, 2 pts. developed stenosis at other sites in the arteries, 2 patients had a complete thrombotic occlusion of the vessel (at 16 & 37 months) and 1 patient underwent surgery at 9 months for a broken stent.

The P.A.R.I.S. Trial (Peripheral Artery Radiation Investigational Study)

"This is a FDA-approved trial testing a variant of the Frankfurt approach in the United States. The study consists of two phases. The initial phase enrolled 40 patients in 4 centers to test the feasibility and safety of this approach. The second phase, which began in early 1998, is the first double blinded, placebo controlled randomized multi-institutional study in this setting. Based on an estimated 30% reduction in restenosis at 12 months, 300 patients will be accrued from 12 centers across the United States. Eligibility criteria include patients aged 40 - 80 years with Rutherford category 2 or greater claudication, or evidence of leg ischemia at rest or after exercise and an abnormal ankle-brachial index (ABI). Target lesions should be suitable for PTA, without stenting (the FDA has not approved any stents for femoropopliteal applications in this country), and have the following characteristics: (i) stenosis between 5 - 15 cm in length, (ii) combined stenosis and occlusion of 5 - 15 cm, with the totally occluded segment less than 5 cm in length, (iii) lesion length of 5 - 10 cm for a 4 mm artery, and 5 - 15 cm for arteries 5 - 8 mm in diameter, and (iv) at least 1 patent vessel providing straight runoff to the foot.

The radiation is delivered through a specially designed double lumen centering catheter using a HDR Ir-192 stepping source which is delivered to the target site by the micro Selectron ™-HDR remote after loader. One lumen of the catheter is open ended and accommodates the

guidewire. Once the catheter is appropriately positioned in relation to the target, the guidewire is withdrawn and replaced by the closed ended radiation sheath (with a stiffening mandrel), which serves as a channel for the active or dummy source. This radiation sheath accepts a 6 Fr. adapter for connection to the microSelectron (channel 1). The other lumen serves to inflate a segmented balloon (Fig. 13.1a - d) - the balloon centers the source within the vessel lumen, while the segmented nature of the balloon maintains this centering (without getting kinked) even when the path of the catheter is angulated (Fig. 13.2). The target length is defined as the total length of the intervened ("injured") segment plus a margin of 1 cm on either side. The "active treatment length" or the length over which the source "steps" includes an additional 0.5 cm on either side to allow for the "penumbra effect" (Fig. 13.3). A dose of 14 Gy is prescribed to the adventitia, which is presumed to be at a distance of 2 mm from the balloon surface; thus the dose is prescribed at a distance equal to the radius of the balloon + 2 mm (AAPM TG-60 recommendation).

Following a successful angioplasty, the catheter is positioned in the artery under fluoroscopic guidance and secured properly to the skin. The patient is then transported to the radiation oncology department, where the position of the catheter is verified by confirming the relation of the distal radio-opaque marker on the catheter to a graduated radiopaque scale on the patient's thigh (Fig. 13.4, 13.5). Patients are randomized to the "placebo" or "radiation" arms (the software of the afterloader is specially adapted to allow for the delivery of a full treatment with the dummy source). The balloon is inflated and the catheter is then connected to the afterloader for the delivery of the treatment (Fig. 13.6). After completion of the treatment, the catheter is

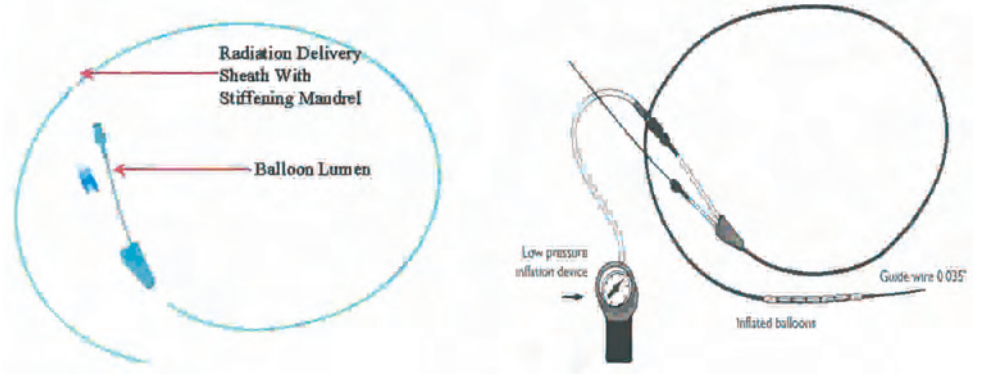
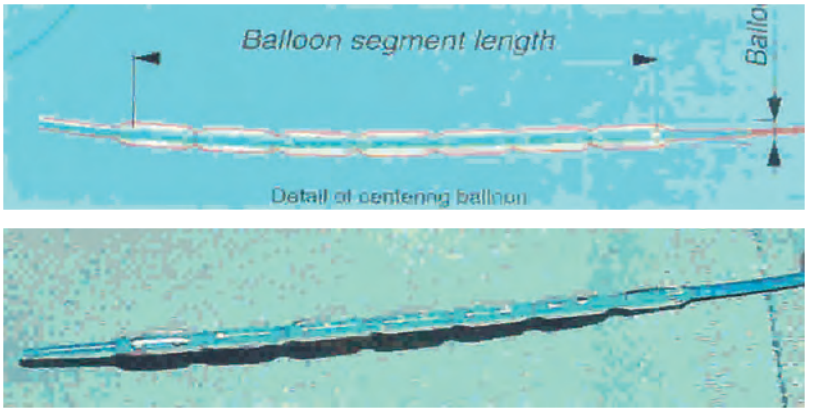


Figure 13.l a, b, c, d: The PARIS catheter. Courtesy Nucletron Corporation



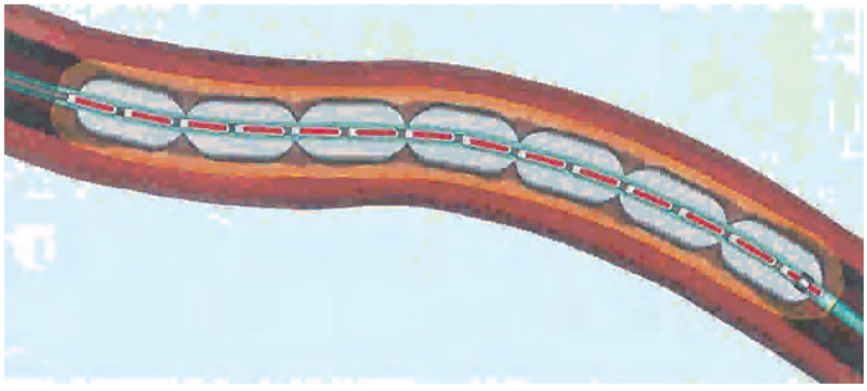


Figure 13.2: Segmented balloon catheter showing the centering of the source. Courtesy Nucletron Corporation

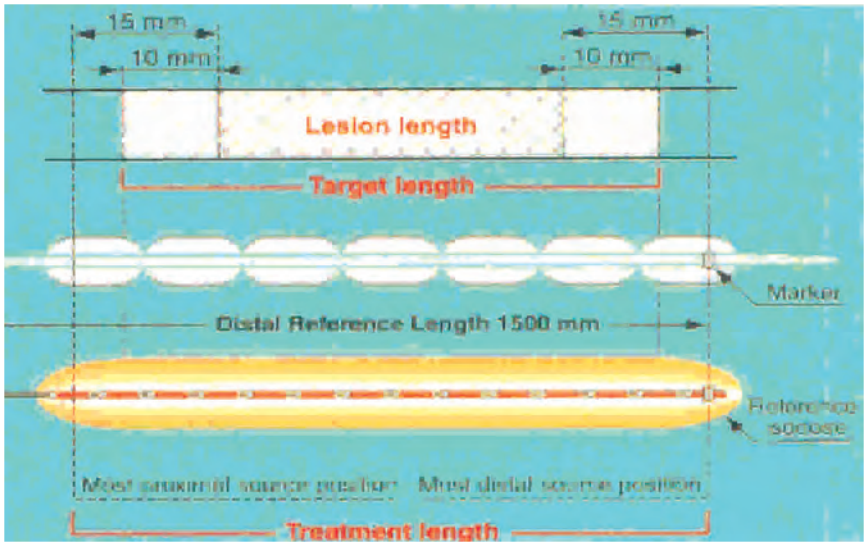


Figure 13.3: Determining the treatment length in the PARIS trial. Courtesy Nucletron Corporation

Figure 13.4: PARIS case showing the radio-opaque graduated ruler and the lead BB on the patient's skin. Courtesy Dr. Prabhakar Tripuraneni, Scripps Clinic. La Jolla, CA

disconnected from the afterloader, the balloon is deflated, and the patient is transported back to the Radiology suite for removal of the catheter and usual after-care.

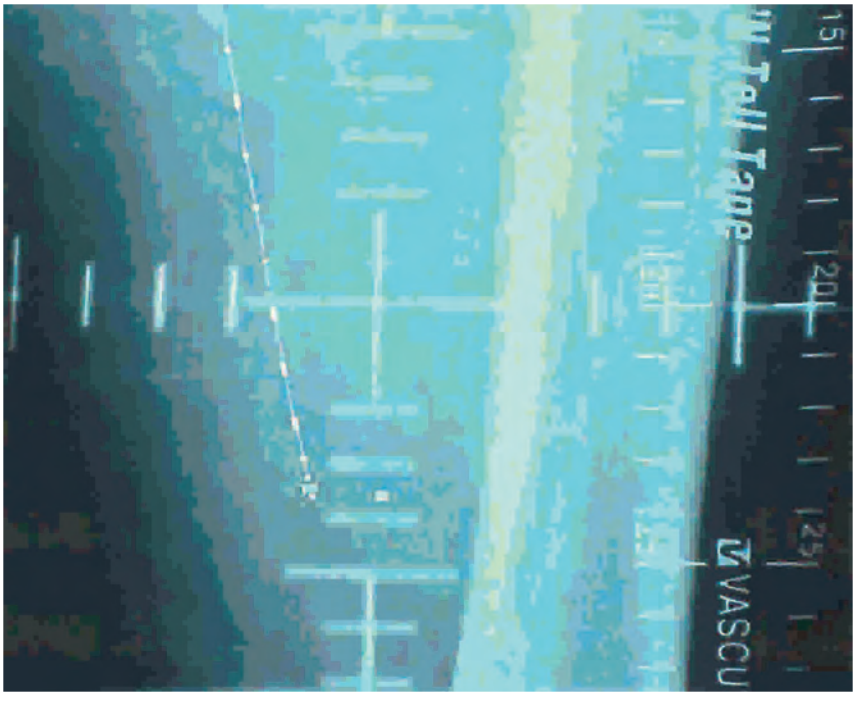


Figure 13.5: Simulation film of a PARIS case, showing the graduated radio-opaque scale on the right, and the proper alignment of the lead BB on the patient's skin with the distal end of the dummy source within the PARIS catheter. Courtesy Dr. Prabhakar Tripuraneni, Scripps Clinic. La Jolla, CA

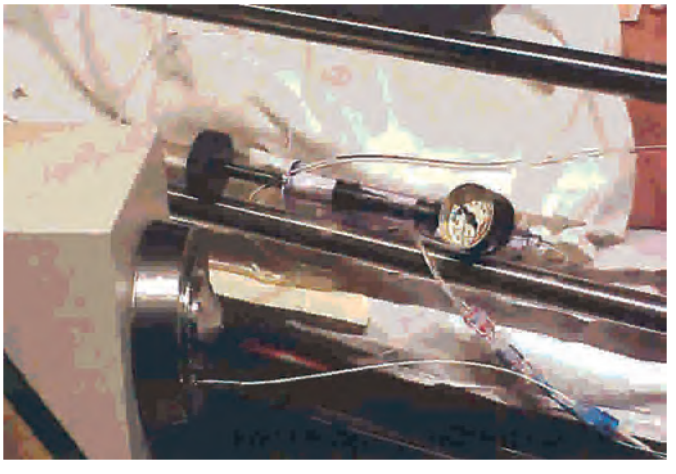


Figure 13.6: PARIS case in progress. Courtesy Dr. Prabhakar Tripuraneni, Scripps Clinic. La Jolla, CA

The preliminary results of the 40 patients enrolled in the feasibility phase are very encouraging: radiation delivery was feasible in all but 1 patient; there were no procedure-related complications. Mean lesion length was 8 cm. At follow-up, maximum walking time on the treadmill increased from 3.56+/-2.7 min. to 4.53+/-2.7 min. (p=0.0l) and the ABI also increased from 0.7+/-0.2 to 1.0+/-0.2. The 27 patients who had an angiographic follow-up at 8 months

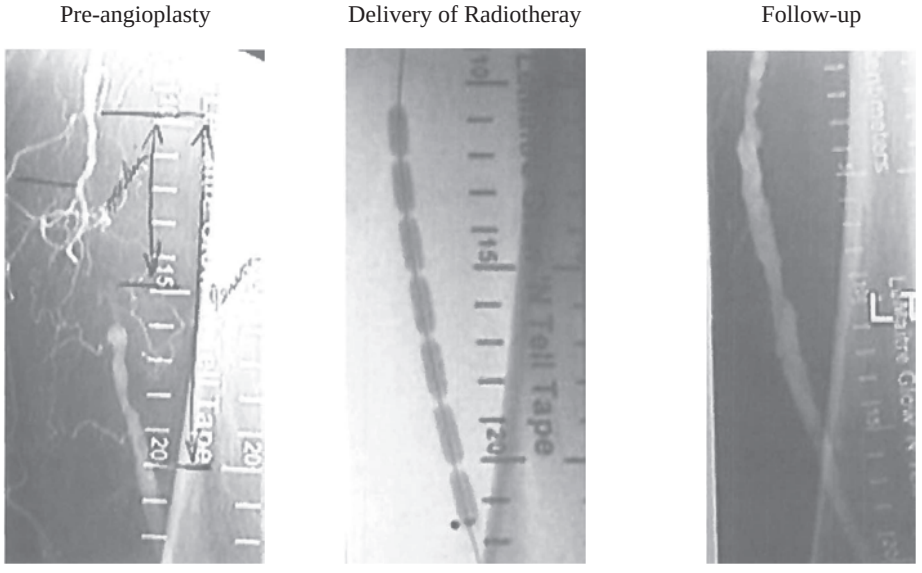


Figure 13.7: Example of a PARIS case .. From Tripuraneni P, Giap H, Jani S. Endovascular Brachytherapy for Peripheral Vascular Disease. Sernin Rad Onco11999. W. B. Saunders Company. With Permission.

showed a restenosis rate of only 11 %. Also, in 70% of the patients, dissections had been observed on the immediate postprocedural angiogram (stenting was not allowed in this protocol). Follow-up angiograms showed complete healing of all of these dissections with no pseudoaneurysms - Fig. 13.7 (9).

The randomized phase of PARIS was initiated in 15 centers in 1998 and enrollment of the patients should be completed at the end of 2000. The primary endpoint is angiographic absence of restenosis of the irradiated vessel at 12 months. Other parameters include improvement of treadmill exercise time of greater than 90 sec and a sustained improvement in the resting ankle-brachial index by greater than 0.1 when compared to the pre-PTA value (at 6 and 12 months follow-up).

The Vienna Experience (l0, 11)

In May 1996, Minar, Pokrajac et al (in Vienna) began investigating the feasibility and efficacy of endovascular brachytherapy following femoropopliteal angioplasty. All trials employed an Iridium-192 source with a diameter of 1.1 mm delivered by a high-dose-rate remote afterloader (micro-Selectron™; Nucletron).

Vienna 01 Trial

In this pilot study, 10 patients with long-segment (mean length: 16cm; range: 9-22cm) restenosis were treated with PTA followed by endovascular brachytherapy. A dose of 12 Gy was prescribed to the inner intimal layer of the vessel. Follow-up examinations included measurement of anklebrachial- index and color duplex sonography with calculation of the peak velocity ratio; angiography was performed in patients with a suspected recurrence. In six patients, the dilated and irradiated segment remained widely patent on color duplex sonography,

with corresponding excellent hemodynamic and clinical results at 12 months. In four patients, arteriography demonstrated 60 - 90% diameter restenosis. This was a cohort of patients at a particularly high risk for restenosis with conventional interventional techniques; in this context, the results of the pilot study were very promising (12).

Vienna 02 Trial

From November 1996 to August 1998, 113 patients with femoropopliteal stenoses/ occlusions were enrolled in this randomized trial comparing PTA plus brachytherapy (N=57) versus PTA alone (N=56); none of the patients had any stent implantation (13). Patients with de novo lesions > 5 cm and recurrent lesions of any length were eligible. The mean treated length of the artery was 16.7cm (PTA + brachytherapy) vs . 14.8cm (PTA). In patients randomized to PTA + brachytherapy, a dose of 12 Gy was delivered at a distance of 3 mm from the source axis using the high dose-rate remote afterloader with an Ir-192 source. The irradiated length consisted of the total intervened length plus a margin of 1 cm on either end. No centering devices were used. The mean irradiation time was about 4 minutes. The protocol, including transportation to and from the brachytherapy unit, added an average of 30 minutes to the interventional procedure. Follow-up examinations included measurement of the ankle-brachial-index, color-flow duplex sonography and angiography. The primary endpoint of the study was vessel patency at 6 months.

The irradiation procedure was technically feasible in all patients without complications. 107 patients were available for angiographic follow-up at 6 months. The dichotomous angiographic recurrence rate was 15/53 (28.3%) in the PTA + brachytherapy group Vs. 29/54 (53.7%) in the PTA alone group (chi-square test; $p < 0.05$). The cumulative patency rates at 12 months follow-up were 63.6% in the PTA + brachytherapy group and 35.3% in the PTA alone group (log rank test, $p < 0.005$).

This is the fIrst randomized study to demonstrate the efficacy of endovascular BT in preventing restenosis after femoropopliteal PTA. Despite the signifIcant reduction of restenosis in this randomized trial, the overall rate of restenosis rate is still high. This may be due to a lower nominal dose (12 Gy) than that employed in most intracoronary trials using gamma sources (14 - 15 Gy). Another important factor may be the dose inhomogeneity due to an eccentric catheter lie (as a result of non-centering). An eccentric plaque can further accentuate this non-centering, resulting in signifIcant dose inhomogeneity to the target volume. Although some centering may be achieved by the 5-Fr. radiation delivery catheter and the 6-Fr. sheath, review of these cases showed noncentering in a signifIcant number of patients.

The angiographic pattern of restenosis observed after brachytherapy was quite different from the typical restenosis seen after long-segment angioplasty without brachytherapy. The classic pattern of post-PTA recurrence after long-segment PTA is a diffuse restenosis involving most of the former dilated segment. In contrast to this, patients presenting with restenosis after brachytherapy often had one or more segments of focal stenosis with "normal" intervening segments. This observation lends further support to the hypothesis that areas of underdosing due to dose inhomogeneity may well be the cause of failure in many of these patients. In contrast to the results from intracoronary trials, "edge effects" or "marginal failures" were not observed in these patients. This may be due to the meticulous delineation of the target length, taking care to include the entire intervened vessel length plus a "safety margin" of 1 cm on either side. Late thrombotic occlusion was also not a problem in this study.

Vienna 03 Trial

This study uses a centering catheter and is designed as a randomized double-blinded study comparing the restenosis rate after PTA + brachytherapy Vs. PTA alone. However, in contrast to the PARIS protocol, patients with longer lesions (total occlusions > 5 cm) are eligible and the prescribed dose is 18 Gy delivered to the adventitia of the artery. The primary endpoint is angiographically demonstrable restenosis. More than 100 patients have already been enrolled on this study.

Vienna 04 Trial

To evaluate the interaction of endovascular brachytherapy and arterial stenting, the Vienna group has completed a pilot study in patients with long-segment femoropopliteal angioplasty plus stent implantation. 33 patients were enrolled between October 1998 and June 1999. The mean treated length was 17 cm. A dose of 14 Gy was prescribed at 2mm beyond the average luminal radius using the PARIS centering catheter. All patients received clopidogrel 75mg/day for one month (following a loading dose of 300mg in the catheter laboratory immediately after stent implantation) and were maintained on long-term aspirin (100mg/day). The 6-months angiographic results demonstrated excellent angiographic results in 23/33 (70%) patients, while 10/33 patients (30%) had a target lesion failure. Three patients presented with stenosis, and 7 with sudden late thrombotic occlusion of the stented segment, occurring between 3.5 and 6 months after the intervention (most of these did not have restenosis, as evidenced by a patent vessel following thrombolysis). This is in keeping with the coronary experience of late stent thrombosis. Therefore, all patients are now maintained on clopidogrel for 6 months.

Vienna 05 Trial

Based on the Vienna 04 pilot study, a double-blind randomized trial has been opened to compare the angiographically verified recurrence rate after femoropopliteal stenting and brachytherapy vs. stenting alone. The study began accruing in June 1999. Study design and dose prescription are identical to the Vienna 04 trial; all patients will receive clopidogrel for at least one year. More than 60 patients have been enrolled in this ongoing trial.

Other Endovascular Femoropopliteal Trials

Switzerland Trial (14)

A Swiss group, in Bern, has initiated a three-phase trial in 1997 investigating the role of endovascular BT in femoropopliteal lesions. Phase I aims to evaluate the feasibility of brachytherapy dose of 12 Gy prescribed at a radial distance of 3 mm. The second phase of this study, which was initiated concurrently with the first, looks at "dose escalation" - the same 12 Gy is prescribed to a radial distance of 5 mm. Phase III consists of a four-arm trial randomizing patients to a) PTA + aspirin, b) PTA + aspirin + brachytherapy, c) PTA + aspirin + probucol, or d) PTA + aspirin + probucol + brachytherapy. A total of 320 patients will be enrolled (80 in each arm) and a dose of 14 Gy will be prescribed at the reference radius + 2 mm. Proximal and distal margins of 10 & 20 mm (respectively) will be used. No centering device or stents will be used. Patient accrual is still under way.

Rotterdam Trial

The VARA Trial is currently underway in Rotterdam. The study design is similar to the PARIS trial and employs a centering device.

OTHER SITES

TIPS (Transjugular Intrahepatic Portosystemic Shunt

This procedure is used in patients with portal hypertension to decompress the portal venous system, to alleviate the symptoms of variceal bleeding and ascites. The technical success rates with TIPS are reported to be as high as 95%, but stenosis at the stent margins, due to neointimal hyperplasia (NIH), limits its long-term utility. Thus, a retrospective review of 1750 patients from 9 institutions reported a stenosis rate of 29% at 6 months, 42% at 12 months and 51 % at 24 months. The major cause for this is NIH formation within the stent. Though these patients can, and do, undergo repeated balloon angioplasties and stenting, the interventions subject the patient to significant risks, and are associated with significant costs.

Cejna, Pokrajac et al from Vienna reported on 5 patients with a history of at least 1 prior TIPS revision. Patients were treated with HDR brachytherapy employing a remote afterloader; a dose of 12 Gy was prescribed at a distance of 5 mm from the source axis. In the 2 patients with Budd-Chiari Syndrome, further revisions were necessary at 168 and 535 days following the radiation. However, in the other 3 patients, the shunt remained patent 90 days to 3 years following the brachytherapy (15). The SCRIPPS Clinic has obtained FDA approval for a pilot study on 15 patients. The brachytherapy will be delivered using an Ir-192 HDR remote afterloader, with a dose of 1000 - 3000 cGy being prescribed based on IVUS measurements (16).

Other Potential Sites

Tibio-Peroneal Arteries: These are much smaller arteries and the disease pattern is often multifocal or diffuse. The results with most forms of conventional intervention are unsatisfactory. To date, there has been no clinical data reported on the use of radiotherapy for tibioperoneal disease; given that the basic process is one of NIH, and some of the preliminary observations form the SCRIPPS trial (i.e. intracoronary brachytherapy is more effective in smaller vessels and possibly diabetics), it is very likely that EVBT would playa significant role in this setting as well.

Renal Artery Stenosis: This is a significant cause of hypertension, especially in patients with multiple manifestations of atherosclerotic disease. A large number of patients (> 15%) above the age of 50 on chronic dialysis also have renal artery stenoses. Medical control of hypertension can be quite difficult in these patients. Surgical treatment of these lesions is possible, but it involves a major procedure with a high peri operative morbidity and mortality. From an angioplasty point of view, there are 2 groups of patients - ostial lesions and non-ostial lesions. The former are more refractory, and are often treated with additional stenting, following a PTA. Overall, the restenosis rates range from 20 - 30 % in the best of series. Once again, NIH is the major culprit and EVBT should be explored in this population.

Iliac Arteries: While some of the early animal work was done in rabbit iliac arteries, the clinical restenosis rate in this setting, especially with the addition of stenting, is quite low. However, there are selected sub-groups that do not do so well. These include total occlusions, patients with poor run-offs, and patients with combined common iliac and external iliac lesions. These may warrant further study with the addition of post-PTA (+/- stenting) EBRT.

Subclavian Veins: Subclavian vein catheterization is associated with a stenosis rate of 40 - 50%. These stenoses are particularly refractory, and even stents are associated with a 1 year

patency rate of only 25 - 40%. Also, a stenosis in the subclavian vein essentially renders the entire venous "tree" in that arm "useless" for dialysis access. Apart from the preliminary data from Emory (16) and another case report (17), there is no clinical trial data in this setting.

Summary

Peripheral vascular insufficiency, while rarely life-threatening, is often be limb-threatening, and has major implications for the patient's quality of life. The magnitude of the problem is at least as great as that of coronary artery disease. Unfortunately, though endovascular brachytherapy was first performed in the femoropopliteal arteries, the majority of the subsequent clinical studies have focussed on the coronary problem. The PARIS trial has also been quite slow to accrue patients. On this background, it is heartening to see the rapid accrual of patients in the European trials, especially those conducted at Vienna. The Vienna studies have confirmed the principle of endovascular brachytherapy in the femoropopliteal arteries, and the ongoing studies will serve to refine the use of this technique in this group of patients. There are several other peripheral sites where vascular radiotherapy may be useful, and it is imperative that well designed clinical trials be conducted in these patient populations. Only then will we be able to establish the role of vascular radiotherapy in these challenging clinical problems.

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14

Vascular Access for Hemodialysis

Background

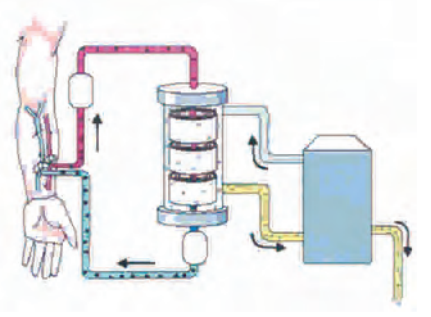


Figure 14 .1: Sc he rnat I' C 0f H emo ct·l a IY SI.S

The full potential of hemodialysis was limited for years by the absence of a means for repeated access to the vascular system. At the outset, it was necessary for repeated cutdowns to be made on the artery and the vein for each dialysis, following which the vessels were ligated. The duration of a course of dialysis was limited to the treatment of acute renal failure. Successful, longterm hemodialysis (Fig. 14.1) requires a vascular access that is readily available, and sustains a high blood flowrate to allow uninterrupted shunting of atleast 200 ml/min without thrombosis. The number of patients requiring such a vascular access for hemodialysis has continued to increase over the years. Currently, there are over 250,000 patients on long-term hemodialysis in the United States alone. In addition, almost 50,000 patients require the initial creation of chronic vascular access annually, while another 25,000 patients require at least one operation for revision of their existing access in the same year. Such an access is usually achieved by the surgical creation of an arterio-venous fistula.

Physiology of Arteriovenous Fistulas

A fistula may be formed directly between an adjacent artery and vein or, if these vessels are separated, by connecting them with a conduit limb of variable diameter and length. In all fistulas, the direction of flow in both the proximal artery and vein is normal. Fistulas for therapeutic purposes are usually large (fistula diameter greater than 75% of the arterial lumen) and the blood flow in the distal artery and vein is usually reversed. When a fistula is opened, there is a fall in the peripheral resistance, which leads to an increase in cardiac output. The proximal arterial flow is increased, and accompanying this, there is an increase in the proximal venous outflow. The highest pressure in the distal artery is usually only two-thirds of systemic pressure, which is still higher than the pressure at the fistula opening, leading to a retrograde flow in the distal artery. Blood in the distal fistula vein flows retrograde until at some point the valves are able to withstand the pressure. The blood in the distal vein is carried cardiad by venous collaterals which open off the vein. With time, there is significant increase in the number of collateral vessels

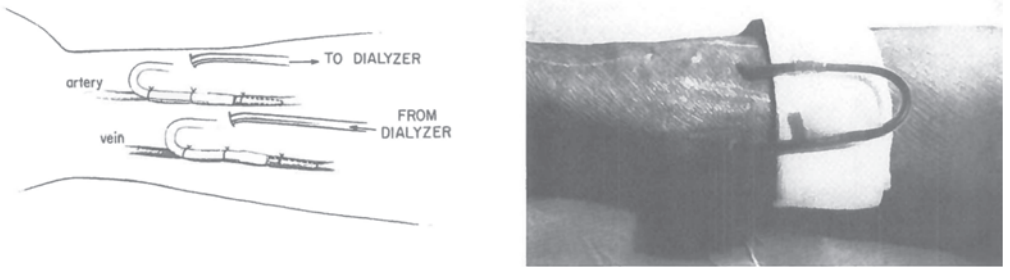
formed between the proximal & distal arteries and the proximal & distal veins. In addition to this, there is a lengthening and dilatation of the proximal & distal veins and the proximal artery. The proximal artery develops smooth muscle hypertrophy in addition to dilatation, and then elongates. Later the muscle atrophies and the vessel becomes tortuous and aneurysmal. The veins continue to dilate for up to 8 months, and gradually get arterialized and tortuous.

Types of Access

External Arteriovenous Shunt

The development of the external arteriovenous shunt in 1960 provided the fIrst successful method for long-term access to the circulation for hemodialysis. Quinton, Dillard and Scribner described their technique (Figs. 14.2A, B), which basically consisted of a loop of Silastic tubing lying on the volar aspect of the forearm, connecting Teflon cannulas in the radial artery and nearby wrist vein (1). Numerous variations of this were subsequently described - the Ramirez shunt, the Buselmeier shunt, the Thomas shunt, etc.

Although quickly and widely adopted as a practical means of providing access in chronic renal failure, several disadvantages soon became apparent: 1) a high rate of infection due to bacterial contamination at the entry sites in the skin; 2) frequent thrombosis of the shunt due to the small size of the conduits; 3) restriction of the patient's daily activities; and 4) utilization of vessels and vascular sites potentially available for more permanent vascular access. Consequently, these are rarely used today.



Figures 14.2A, 14.2B : An example of a Scribner Shunt From "Vascular Access - A Practical Guide", ed. M. Haimov; with pennission from Futura Publishing Company, Armonk, NY

Autogenous, Subcutaneous AV Fistula

This was first described in 1966 by Brescia, Cimino, Apel and Hurwich and is currently the procedure of choice (2). Is associated with the longest useful patency and lowest rates of infection, and is least likely to thrombose; the fistula is also unobtrusive and does not interfere with patient activities. It does, however, require an artery large enough to support a high rate of blood flow, and veins that will arterialize and dilate. Also

Figure 14.3 : Vessel Configurations in The Cimino Fistula

it takes about 3 - 5 weeks after fistula construction for the veins to mature into the large, thickwalled vessels that can be repeatedly and reliably punctured. During this period of time, dialysis may be maintained using a Scribner shunt, central venous cannulation or by peritoneal dialysis. The fIstula is most commonly constructed between the radial artery and the cephalic vein at the wrist of the non-dominant hand, though several variants have been described. At surgery, under local anesthesia, the radial artery and cephalic vein are mobilized and anastamosed in one of four different configurations (Fig. 14.3). The Cimino fistula may function for a long time. Eventually it can fail due to sclerosis of the veins as a result of repeated venipunctures or following renal transplant, when changes occur that restore coagulation to normal.

Vascular Grafts (Bridge Fistulas)

Vascular substitutes are used in access surgery when suitable arteries or veins are not available for the construction of a standard peripheral AV fistula. There can be several reasons for this: 1) the peripheral vessels have already been used for previous access procedures; 2) the peripheral veins have been rendered unusable by drug abuse or intravenous therapy; 3) severe peripheral vascular disease exists, especially in diabetics; 4) obesity with inadequate superficial veins.

These fistulas take on various configurations (Fig. 14.4). If the vein and artery are close to each other, the bridge material may run in a loop or lie in a U configuration. If the artery and vein are some distance apart, the bridge graft lies in a straight or curved line. Bridge fistulas can be placed between almost any suitably sized superficial artery and vein in the body. After implantation, these easily palpable conduits can be readily punctured by needles for dialysis. Because of a lower risk of infection, and distal limb ischemia, location of the fistula in the arm is almost always the first choice (traditionally between the radial artery & cephalic or basilic vein, or between the brachial artery & cephalic or basilic vein), and is mandatory in the older patient with leg vessel atherosclerosis, or the obese patient with groin dermatitis. Both biologic and prosthetic materials have been used in the creation of bridge fistulas. The biologic materials include autogenous/homologous saphenous vein grafts, human umbilical veins and bovine carotid arteries. These are not commonly used due to problems with graft material degeneration with aneurysm formation, anastamotic stenosis and thrombus. Prosthetic materials employed include Dacron velour and expanded PTFE. Expanded PTFE is the most commonly used material today for bridge fistulas. These grafts do not require pre-clotting, are widely available are easily inserted, easily thrombectomized or recanalized (with reasonable patency), have a moderate resistance to infection and a low incidence of aneurysm formation (3). The usual graft diameter is 6 - 8 mm though tapered grafts are often preferred to minimize graft-vessel mismatch.

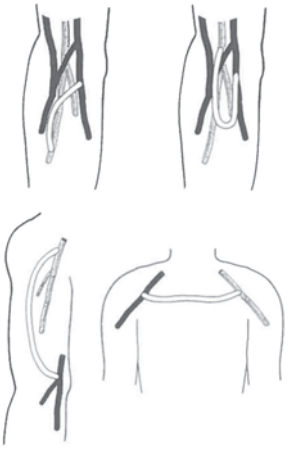


Figure 14.4 : Upper extremity bridge arteriovenous fistulas

Complications

Unfortunately, these vascular accesses have a significant incidence of complications (4). Complications associated with arteriovenous access are the most common cause of hospitalization for patients on chronic hemodialysis, who require, on an average, 1 month hospitalization each year; about half of this time is for placement or revision of their arteriovenous communications. Preservation of access sites is of paramount importance as patients are being carried on hemodialysis for longer periods (almost 50% at 5 years). Understandably, vascular access has been referred to as the "Achilles heel of the hemodialysis patient" (5). The most common complicationis partial or complete obstruction of the access blood flow due to thrombosis or vascular stenosis - these account for over 80% of all complications. Less common complications include, aneurysm and pseudoaneurysm formation, steal syndrome, distal extremity edema, high-output congestive heart failure and infection.

Pathophysiology of Access Failure

Stenosis at or near the venous anastamosis is the most common cause of late-access failure. The Brescia-Cimino fistulas have up to a 90% useful patency at 12 months, dropping to about 70% by 48 months. Romero et al (6), in a study of Cimino fistula thrombosis, found that 17% of thrombosis were due to arterial stenosis within few millimeters of the anastamosis, 35% were due to venous stenosis within a few centimeters of the anastamosis, and 35% were due to both arterial and venous stenosis. In 13% of the cases no cause could be found for the thrombosis.

The available literature on the pathophysiologic mechanisms responsible for this stenosis/failure is surprisingly scanty. Early failure due to thrombosis can be a result of surgical trauma, twisted veins, adventitial bands, and veins with proximal stenosis or sclerosis from previous phlebitis (7, 8). Delayed failure is usually due to neointimal intimal hyperplasia (NIH), secondary to high blood flow, turbulence, and shear stresses (9, 10). The process has been compared to that causing stenosis/obstruction in coronary artery bypass vein grafts (however, it should be appreciated that a vein segment that has been harvested to use as a vascular graft at a distant site, e.g. a coronary bypass graft, may behave quite differently from a vein that is left in situ without significant alteration in its blood supply, as is the case with the dialysis accesses). The cells of NIH have ultrastructural features of smooth muscle cells (SMC), lying within an acid mucopolysaccharide mucoid matrix. These SMCs are most likely of medial origin. While the exact pathogenesis of NIH remains speculative, the essential process is one of phenotypic modulation of the contractile SMC into a predominantly proliferative/secretory SMC (11). Numerous mechanisms have been postulated for this process:

Role of vascular injury

Vascular injury may promote SMC proliferation by antagonizing the growth inhibitory processes of the undamaged vessel wall. The endothelial denudation results in the loss of the growth-inhibitory heparin-like glycosaminoglycans and several mitogens are known to be released from damaged endothelial cells as well as the SMCs. The operative procedure can lead to loss of the vasa vasorum during the mobilization of the vein. The relative ischemia and resultant SMC necrosis can cause a compensatory proliferative response in the remaining SMCs (12).

Platelet-vessel wall interaction

SMC proliferation also occurs in response to platelet-borne mitogens. Adherence of platelets to a site of injury is followed by release of the contents of their alpha-granules; these include the platelet-derived growth factor (PDGF), epidermal growth factor (EGF), beta-transforming growth factor (beta-TGF) , platelet factor 4, etc. PDGF may be the key to the entry of the SMC into the cell cycle, while progression into the active phase of replication may depend on somatomedin-C production by the SMC itself (13).

3) Altered local hemodynamics

Venous limbs of the AVFs are distended by high arterial pressures that cause increased circumferential and radial stresses. The distribution of these stresses has been found to correspond to the distribution of proliferative wall thickening in a dog model. Cyclic stretching also stimulates synthesis of matrix components by cultured smooth muscle cells. Given that the pulse pressure is considerably greater in the arterial circulation, the increased cyclic stretching to which the veins are subjected may play a role in this secretory function of the SMCs (14 -17). The flow dynamics in the venous limb may also modulate the extent of the NIH. Low flow rates have been associated with a higher incidence of NIH. The flow velocity is directly related to blood-vessel shear stress, an important factor in detennining the probability and duration of adherence of blood-borne elements to the intima. Thus, low wall stress can augment the SMC proliferation, possibly mediated by release of mitogenic factors from adhered platelets and monocytes that stimulate SMCs to proliferate and migrate (18,19). Turbulence of flow at the anastamosis may enhance the proliferative response in the vein, most likely by causing recurrent localized endothelial disruption. Lastly, it has been suggested that the mismatch in compliance between the artery and the vein, at the anastamosis, may be a factor in causing intimal damage and secondary NIH (20,21).

Miscellaneous factors

The role of elevated lipids and systemic hypertension in the development of NIH is unclear. Numerous other factors have been incriminated in the NIH on the arterial side. Whether the same factors are operational in the venous system or not is pure speculation, at this point.

In cases of PTFE graft failure, venous anastamotic stenosis is found in 60 - 80% of the cases, while arterial stenosis occurs in 10 - 20% of the cases. The long-tenn follow-up with PTFE grafts reveals a one year patency rate of about 60% and a two year patency of only 40% (22). The basic underlying process causing stenosis at the PTFE venous anastamosis sites is also that of intimal hyperplasia. Soon after the fistula is created, the inner surface of the graft becomes lined with platelets, fibrin and cells. Endothelial cells migrate downward from the vein onto the debris in the graft and eventually form a continuous lining of the proximal 2-3 cm of the graft. Similarly, myointimal cells from the vein migrate, undergo a metaplastic change and form proliferating cells that give rise to the NIH. A recent account gives a detailed description of the histology of intimal hyperplasia causing such stenosis (23). Immunocytochemical stains showed that the intimal hyperplasia consisted of SMCs in an extracellular matrix. The SMCs near the media contained more actin than those near the lumen, suggesting that the latter are younger, less well differentiated, proliferating cells. The authors postulate that the hyperplasia is due to two local factors - the release within the graft of the platelet-derived growth factor (PDGF) and localized intimal injury caused by highly turbulent blood flow at the anastamosis. Based on their work with

tenascin, a newly described extracellular matrix protein, recent studies from Emory University suggest that extracellular matrix may comprise the bulk of occlusive neointimal hyperplastic lesions in PTFE graft failure (24). The tenascins are a family of large multimeric extracellular matrix proteins consisting of repeated structural modules including heptad repeats, epidennal growth factor (EGF)-like repeats, fibronectin type III repeats and a globular domain shared with the fibrinogens. Of the three tenascins, tenascin-C, -R and -X, tenascin-C is prominent during tissue remodeling and is linked to cell migration, proliferation and apoptosis. There is also evidence that the induction of tenascin may be critical to growth factor-dependent SMC proliferation. This indicates that an effective treatment strategy to prevent graft occlusion could be aimed at inhibition of matrix production, without necessarily affecting SMC proliferation or migration.

Less common causes of access failure/thrombosis include intragraft stenosis, volume depletion, hypotension, congestive heart failure and external compression. Proximal venous stenosis is an unusual cause of access failure. This may be due to turbulent flow in a high-pressure vein with resultant accelerated atherosclerosis at the site of venous valves or bifurcations. Alternatively, platelets damaged by the dialysis process can become activated, adhere to the endothelium and initiate the endovenous stenosis. The Venturi effect, which may cause coaptation of the walls of the veins that are not nonnally subject to rapid flow rates and high pressures, may also be related to these lesions. Venous trauma, as a result of venipunctures for cannulation, is probably an additional predisposing factor.

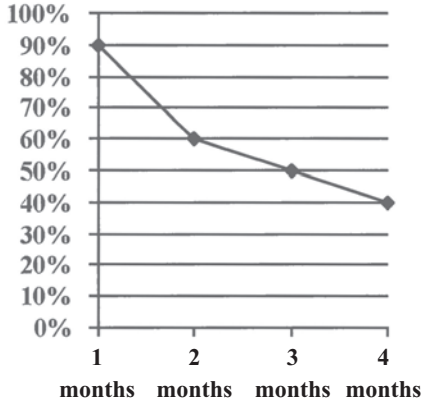


Figure 14.5 - Primary Patency of Dialysis Accesses

Conventional Treatment

The natural history of dialysis accesses is rather dismal due to this high complication rate (Fig. 14.5). Native AV fistulas have a higher primary patency rate once they are functioning adequately. Unfortunately, due to anatomic and other constraints, less than 30% of the patients undergoing hemodialysis have a native AV fistula. Also, almost 30 - 40% of newly constructed native fistulas do not adequately mature and thus cannot be used for dialysis. Expanded PTFE grafts, while more widely applicable, have a mean patency of only 1.7 years (4) - 10 to 20% of newly constructed grafts will fail within 2 months and several centers report 1 episode of graft

thrombosis per patient year. There are several therapeutic options for an access malfunction - Table 1 (25). However, an interventional radiology procedure of some sort, usually a percutaneous trans luminal balloon angioplasty, remains the standard approach to a compromised stenotic access.

Table 1 : Therapeutic Options For Access Malfunction

• Intra-access Urokinase	• Surgical Thrombectomy
• Crossed Catheter Urokinase	• Graft Revision
• Radiologic Thrombectomy	• Jump Graft
• Balloon Angioplasty	• LigationlExcision
• Endovascular Stents	• New Access
• Directional And Pull-back Atherectomy	

Venous angioplasties are technically easy procedures that are performed on an outpatient basis, and the initial, technical success rates vary from 80 - 90%. However, the results are seldom durable - Fig. 14.6 (26, 27). Because of this, assisted patency rates (which include multiple dilatations, stent placements and even surgical revisions) are seldom better than 55 - 60% at 2 years (27).

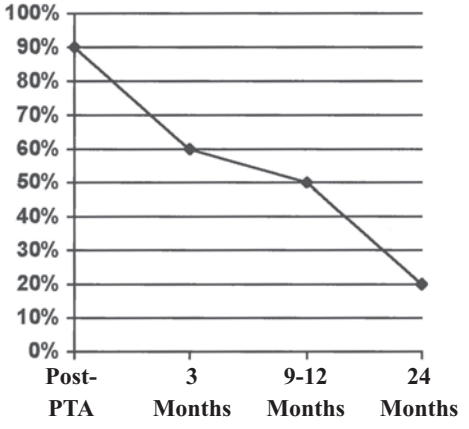


Figure 14.6 : Secondary Patency Of Dialysis Accesses Following PTA

As in the coronaries and in other parts of the arterial tree, pharmacologic adjuvants have had little, if any, impact on the natural history of post-PTA hemodialysis accesses. However, unlike in the arterial circulation, where stents have had a positive impact (28) stents have not provided any long-term benefit to these patients. Stents do help the interventional radiologist by improving the immediate post-PTA patency rates in difficult venous lesions (resistant and/or residual stenoses, long segments, central venous stenosis, etc.), but the results have not been durable (29 - 32). There may be several reasons for this. In the arterial system, stents are believed to act as an "internal scaffolding", thus preventing negative remodeling (this is the late lumen loss as a result of "circumferential constriction" of the arterial wall, a process quite akin to wound contracture). Due to anatomic/structural differences between a muscular coronary artery and the thin walled vein/PTFE graft of the access, it is not clear if this negative remodeling plays a significant role in

continued activation of these factors distinguishes access compromise from post-PTA restenosis in the arteries. With this as a model, it may be unrealistic to expect a pulsed intervention, like post PTA radiotherapy, to "cure" the patient of the restenosis problem. Borrowing some of the oncologic terminology, a more reasonable expectation from post-PTA radiotherapy for these "malignant" restenosis may be a significant prolongation of the "disease-free interval", i.e. a significant prolongation of the time to the next episode of access compromise. Given that about 50,000 patients undergo at least one access revision each year, this would still be a very substantial achievement.

This concept leads to the very important issues of re-treatment and radiation tolerance. If the main goal of radiation therapy is to delay the onset of restenosis, then we have to consider the possibility of re-treating these patients at a subsequent episode of access compromise. Clinical trial design should take account of this - most current laboratory and clinical trials have either a doseescalation protocol, or employ a dose that is supposedly the highest possible "safe" dose. Basic radiation therapy principles, as well as the need for safe re-treatment, make it essential that we determine the lowest possible dose that is compatible with durable freedom from restenosis. Endovascular brachytherapy is again at a disadvantage in this setting; even if the prescribed dose is "low", an iridium-192 based system would deliver almost twice as much to the intima, while a beta-emitter like strontium-90 would give close to four times the prescribed dose to the intima. Radiation tolerance, or late tissue complication probability, also raises the issue of dosefractionation, since a much higher total dose could be delivered with the same late side-effects, if it were delivered in multiple fractions. Again, it is difficult to conceive of an endovascular approach that would allow us to do this. Once again, all these issues can be very easily and effectively addressed by an external beam radiotherapy program (36, 37).

Radiation Therapy To Prevent Post-angioplasty Dialysis Access Restenosis

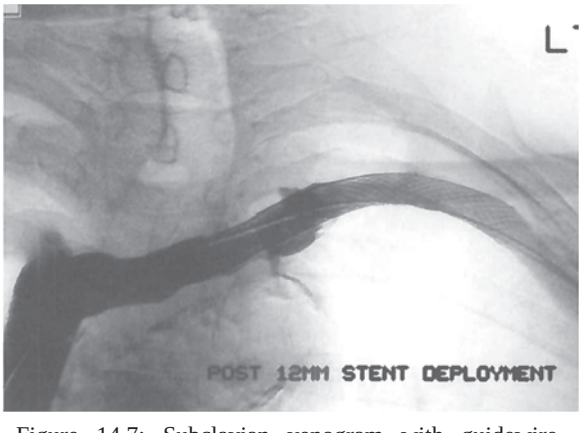


Figure 14.7: Subclavian venogram with guidewire. illustrating the potential for marked non-centering and consequent dose inhomogenenity

Following the reported success of Liermann et al using high dose rate endovascular brachytherapy in the femoral arteries, attempts were made to duplicate their results in the United States. One of the first endovascular experiences was reported by Waksman et al from Emory University. Their pilot study included a number of patients with compromised dialysis accesses. After a successful intervention, a high dose-rate remote afterloader was used to deliver 14 Gy, prescribed to the "adventitia". 18 lesions, including some subclavian stenoses, were treated. At a mean of 44 weeks follow-up, 61 % of the lesions were still patent. One subclavian lesion showed a suggestion of a pseudo aneurysm formation, probably as a result of an eccentric catheter lie

dialysis accesses. On the other hand, it is well known that stents do cause an increase in the neointimal proliferation as a result of the "chronic" injury to the vessel wall by the stent struts (28). Thus, in the coronary arteries, the advantage of preventing negative remodeling outweighs the increase in neointima (resulting in an absolute reduction in the post-PTA restenosis rate by about 15%); however, in the dialysis accesses the problem of increased neointimal proliferation outweighs any possible acute gains, resulting in patency rates with stents that are less than 20% at 2 years. Differences in the structure of the vein wall - especially after it has been chronically subjected to turbulent, high pressure flows - and the relatively low flow states (which increase the neointima formation) may further contribute to the dismal results that are seen with venous stenting. This may be an important difference. There is some evidence to suggest that post-PTA external beam radiotherapy may actually worsen the negative remodeling in the arteries, while still inhibiting the neointimal hyperplasia (33). However, if accesses do not undergo negative remodeling, external beam radiotherapy may be a simple and valid therapeutic option in this setting.

Expectations From Vascular Radiotherapy In The Dialysis Accesses

While the animal and clinical data indicate that intracoronary brachytherapy does indeed deliver durable results, the situation is probably a little different in the accesses. Restenosis in the arterial tree is triggered by the angioplasty "injury". This "trauma" is believed to initiate a series of events culminating in the activation of the medial smooth muscle cell (SMC); this, in turn, proliferates and migrates to form the neointimallesion of restenosis (34). In the arterial system, apart from the PTA injury, there is no ongoing stimulus to the SMC, and any therapeutic maneuver that inhibits the SMC activation/proliferation in the immediate post-angioplasty period, is likely to result in durable inhibition of restenosis. The situation in compromised accesses is quite different (35). The stresses on the vein wall (as a result of altered local hemodynamics) play a major role in access compromise. Turbulent blood flow, increased intraluminal pressures, cyclical stretching of the vein wall in association with the arterial pulse, shear stresses, and mismatched compliances are all very important in the pathogenesis of access compromise. What is even more important is that all these factors continue to act at the anastamosis distinct from the angioplasty injury, and thus constitute a continuous, ongoing stimulus to NIH. This fits in well with the observation by Lumsden et al who studied the pathophysiology of access compromise in PTFE grafts. They found convincing evidence of chronic platelet activation in these patients, as evidenced by elevation of serum platelet factor 4 and /β-thromboglobulin. They also found overexpression of the ligand induced binding sites on the Gp lIb/IlIa receptor (indicative of stimulation of individual platelets) and increased thrombin generation, as measured by serum fibrinopeptide-A and thrombin/antithrombin complexes. They concluded that "..... significant platelet deposition continues to occur in chronically implanted PTFE grafts" (24). Apart from the platelet interaction with the PTFE graft, the extracorporeal circulation through the dialysis circuit is another important mechanism of chronic platelet activation in these patients. Thus, while growth factors, like PDGF (plateletderived growth factor), BFGF (basic fibroblast growth factor), VEGF (vascular endothelial growth factor) and TGF-beta (transforming growth factor-beta) are all involved in this process, the

resulting in inadvertent overdosing of the inner wall of the vein (Fig. 14.7). This data has been reported only in abstract form (38), and details about the exact dose prescription (how was the "adventitial" dose prescription point determined?), post-procedure dosimetry, adequacy of margins etc. are rather sketchy. Also, there have been no further reports on this patient cohort regarding any possible late complications from the therapy. Another report describes a similar endovascular approach for the sequential treatment of two separate lesions in the subclavian vein of a single patient - a durable response was observed out to 15 months (39).

Potential Pitfalls With Endovascular Brachytherapy In AV Fistulas (37)

Need For Source Centering: Most of the early endovascular studies in the coronary arteries have not used a source centering mechanism. The small diameter of the coronary arteries (3.0 - 3.5 mm) and the rapid, pulsatile flow within the artery are arguments used against the need for centering. Similarly, the eccentricity of the plaque is advanced as a reason why centering the source within the lumen would not be useful (since the source would not be centered in relation to the target layer of the vessel wall). The issue of centering becomes very important when endovascular brachytherapy is employed in the dialysis accesses, (and even more so when it is used in the central veins). The average diameter of the vein/graft junction, or the outflow vein is about 6 - 8 mm (the subclavian vein can measure 12 mm or even more). Given the absence of an eccentric plaque, the centering catheter would truly be able to center the source, not only in relation to the lumen, but also with respect to the target layer of the vessel, i.e. true centering would be possible. Also, as discussed above, the lesions can be several centimeters long, and the blood flow through the vein is slower and non-laminar when compared to that through a comparable sized artery. In the absence of a centering system, these factors greatly increase the likelihood of nonhomogeneous dose distribution, both along the long axis and in the radial direction along the circumference of the vein (Fig. 14.8). The Emory study using a noncentered catheter with endovascular high dose-rate brachytherapy in the dialysis accesses had a reported dose variation of 7- 90 Gy (when compared to a prescribed dose of 14 Gy). Thus, not only is true centering possible in the accesses, but it is also necessary for safe and effective therapy.

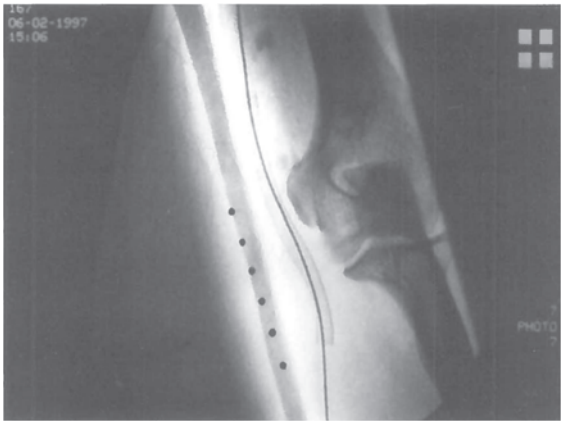


Figure 14.8: Potential for dose inhomogeneity if centering is not employed in larger vessels

Dosimetry Issues: There are several unknown parameters involved in the actual implementation of endovascular brachytherapy in dialysis accesses. The uncertainty about the "culprit" cells or the vessel layer that is responsible for the restenosis, and the paucity of information regarding the vein wall thickness, make it difficult to define the actual prescription point with any degree of confidence. The effect of the PTFE graft material on the dose

distribution is another unknown variable as is the interaction between the centering catheter and the radioactive source. These may be especially important in endovascular brachytherapy with a beta-emitting source, given the very high dose-gradients that are associated with these sources. Thus, while a centering catheter is essential in larger sized dialysis accesses and the central veins, its use, especially in conjunction with a beta-source, needs careful evaluation. Does the catheter "move" the vessel wall further away from the source. Does the distended balloon of the centering catheter cause vessel wall ischemia and make it relatively radio-resistant. Is there an interaction between the beta-source and the different catheter/balloon materials that changes the dose-distribution. These are important issues for study.

Choice of isotope: Radiation protection issues, and the ability to perform the procedure in an unmodified catheterization laboratory make the beta-isotopes a very attractive choice in vascular brachytherapy. However, in the larger vessels, including the dialysis accesses, and especially the larger central veins, gamma-emitters, like iridium-192, are probably preferable. The main reason for this is the less rapid fall off of dose with distance from the source. While this allows us to prescribe the dose at a greater distance from the source, the radial dose fall-off is also less, thus providing a "safety" margin in case the source is not perfectly centered in the lumen. If we assume a 6 mm diameter vessel (the average diameter of the access graft), use a centered Ir-192 source and prescribe 14 Gy to a depth of 2 mm within the vessel wall, the dose at the luminal surface and at a depth of 1 mm would be about 24 Gy and 18 Gy, respectively. Using a strontium-90 source, doses at the same depths would as high as 65 Gy and 30 Gy, respectively. *Of course, external beam radiotherapy would give the most uniform longitudinal, circumferential and radial dose with a very precise dosimetry*.

External Beam Radiotherapy Studies

The superficial location of the accesses makes external beam radiotherapy a very attractive option. A number of pilot studies hint at the potential of external beam radiotherapy in this setting but several fundamental issues regarding the optimal dose, dose-fractionation, timing of radiation therapy, etc. need to be fully defined.

New York Hospital Medical Center of Queens Pilot Study

10 patients were treated in a Phase I study with fractionated external beam radiotherapy as described below. Entry to the study was limited to patients aged 55 years or more, who had a currently compromised access, as evidenced by angiography or a thrombosed access site. All patients had an optimal angioplasty with/without prior thrombolysis, prior to the institution of the radiotherapy. Three patients required placement of a stent to optimize the angioplasty results. Five out of the 10 patients had one or more recanalization procedures performed on the current access. The interval from the last intervention ranged from 2 1/2 months to 14 months. The length of the stenoses ranged from 2 cm to 9 cm, with a median of 5 cm.

Following angioplasty, the interventional radiologist marked the proximal and distal extents of the target on the skin for radiation therapy planning. The depth of the access from the skin was assessed by clinical palpation (since most of these are subcutaneous) and by taking an orthogonal film with a graduated radio-opaque marker on the skin. After all the interventional hardware was withdrawn and hemostasis was achieved, the patient was discharged to the

Radiation Oncology Department. The radiation therapy target volume was defined as the angiographic target lesion plus a 1 cm margin, in keeping with standard radiation therapy principles. An appropriate electron energy was selected by a computerized treatment planning system such that the 90% isodose covered the target volume in all dimensions. Seven patients were treated with 9 MeV electrons, while the other 3 were treated with 12 MeV electrons because of a concern that the proximal portion of the target volume (near the axilla) was a little deeper.

As per the FDA mandate, the first 5 patients were treated with 8 Gy. The second group of 5 patients received 12 Gy. Based on in vitro and animal data, the radiation dose was delivered in 2 equal fractions; the first fraction was delivered immediately post-angioplasty and the second fraction after 48 hours, i.e. on day 2. Follow-up included evaluation of the efficacy of dialysis by recirculation and venous pressure measurements as well as an anatomic evaluation of the fistula by fistulograms, at 3,6, and 12 months intervals. The patients also have a long-term follow up in the Department of Radiation Oncology to monitor any possible late side effects from the radiation therapy. The implementation of the protocol was easy and there were no procedure-related complications. At a median follow-up of 6 months, four patients developed restenosis; three at the site of the original target lesion and one at the edge of an implanted stent. In keeping with the natural history of this process, new lesions developed in 5 patients. Unfortunately, with a longer follow-up, all patients had restenosed by 18 months (40). *This lack of durability is probably a reflection of the patient population as well as the fairly low dose that was used*.

Taiwan Study

Kuan et al reported on 20 patients, each of whom had at least 2 previous episodes of access compromise. These were randomized to PTA alone or PTA followed by external beam radiotherapy to a dose to 1500 cGy in 3 daily fractions. The radiated group showed a two month prolongation in mean access patency time, *a difference that was marginally statistically significant even with the small number of patients* (41).

Temple University Study

Cohen et al. reported on the efficacy of low-dose external beam irradiation in 31 patients with 41 lesions in their dialysis shunts (42). Seven had native arteriovenous fistulas, and 24 had PTFE grafts. The stenoses were either venous outflow stenoses (68%) or central stenoses (32%). The patients were randomized to PTA +/- stent placement alone (N=15) or to the same intervention followed by external beam irradiation (N=16 patients; 21 lesions). A cobalt-60 unit was used to deliver 14 Gy in two 7 Gy fractions; the fust fraction was delivered within 24 hours of the intervention, and the second fraction within the next 24 hours. The restenosis rate at 6 months was 45% in the irradiated and 67% in the control group. However, the patient population was very heterogenous and the patients were not stratified by risk factors. There are also several issues regarding adequacy of margins (treatment planning was based on "lesion length" and not "injured length"), as well as the actual implementation of the radiation therapy (since the patients were planned with the arm in a different position from what it was during the actual treatment). There was no failure analysis to define the contribution of these treatment-related factors to the incidence of target lesion failures (43). Despite these shortcomings, it is very encouraging to note there was clearly a trend in favor of the irradiated patients; the sample size was just too small and heterogeneous to observe a statistically significant difference. Further studies in a larger and more homogenous population are needed to really assess the benefit of external beam irradiation in this setting.

Why Did These Early Studies "Fail" ?

Whether radiation therapy is delivered in 1 fraction, or as a fractionated regimen, the Biologically Effective Dose (BED) is expressed as

$$BED = D\left(1 + \frac{d}{\alpha/\beta}\right)$$

(The precise applicability of the BED formulation for hypofractionatedlsingle fraction regimens is not well established, but this formula does serve as a guide). When one considers the biologically effective doses as outlined in the table below, it is not surprising that the New York Hospital study did not observe any significant benefit from the low doses of 4 Gy x 2 and 6 Gy x 2, and the Taiwan study as well as Cohen et al observed only marginal benefits with 5 Gy x 3, and 7 Gy x 2 (44). The consistently positive results in the coronary/peripheral arterial studies have all been obtained with doses in the range of 12 - 14 Gy. Also, these are prescribed doses, delivered at a depth in the vessel wall; the inner layers of the vessel wall (which may well constitute the radiation target) get even higher doses. Based on the BED analysis, 2 daily fractions of 8 Gy and 3 daily fractions of 7 Gy are likely to be equivalent to these brachytherapy doses (Table 2). These doses have a BED_{acute} (a measure of restenosis inhibition) equivalent to brachytherapy doses of 12 - 14 Gy, while the BED_{late} (a measure of potential late complications) is actually less than that with the brachytherapy doses (i.e. these doses should result in less late tissue changes when compared to brachytherapy).

Table 2

Examples Of Biologically Effective Doses (BED) Employed In Vascular Radiotherapy Studies

	BED (Acute — Efficacy)	BED (Late — Side Effects)
20 Gy x 1 (START) -β radiation	60	153.33
18 Gy x 1 (BetaCath) - β radiation	50.4	126
16 Gy x 1 (START) - β radiation	41.6	101.33
15 Gy x 1 (WRIST) - γ radiation	37.5	90
14 Gy x 1 (BetaCath) - β radiation	33.6	80
7 Gy x 2 (Cohen et al)	23.8	46.6
5 Gy x 3 (Kwan et al)	22.5	40
6 Gy x 2 } (Parikh, Nori)	19.2	36
4 Gy x 2 } (Parikh, Nori)	11.2	18.6
7 Gy x 3 } (RENAL Study)	**35.7**	**70**
8 Gy x 2} (RENAL Study)	**28.8**	**58.6**

Based on this the New York Hospital Medical Center of Queens has initiated the FDA-approved **RENAL** (**R**adiation to **E**xte**N**d **A**ccess **L**ife) study. This incorporates an initial dose-escalation phase (8 Gy x 2, and 7 Gy x 3) followed by a randomized, multi-institutional study.

There are several other ongoing studies in this area evaluating the efficacy of external beam radiotherapy in prolonging access patency. The New York Presbyterian Hospital (Columbia) has a Phase I study in patients with de novo AV grafts. 2 weeks post-surgery, patients have a baseline venogram and 4 weeks post-surgery the patients are treated to either a single dose of 8 Gy, or 2 fractions of 8 Gy each (on consecutive days), using electrons (45). 20 patients will be enrolled in this study. The Duke University has a similar dose-finding Phase I study testing a single fraction of 8 or 10 Gy in the de novo setting with the radiation scheduled to be delivered 1 - 3 days postsurgery. Levendag et al are conducting a double blinded, randomized study employing two daily fractions of 9 Gy each Vs no further treatment (Levendag P. Personal communication). The study is still under accrual.

Summary and Conclusions

There are several unique issues involved in radiation therapy to dialysis accesses. Given the uncertainties of the dose-prescription point, the need for centering an endovascular source, and the smaller margin of safety with the beta-sources, it is likely that any endovascular approach will have to use a gamma-emitting isotope, like iridium-192. This approach has its own logistical problems. Radiation safety is an issue if the procedure is to be done in the interventional suite; furthermore, this precludes the use of a remote high dose-rate afterloader. On the other hand, if the radiation is to be delivered in the radiation oncology suite, there are important issues related to patient transportation with intravascular catheters in place, infection potential, etc. Endovascular approaches have the inherent problem of a radial dose gradient across the vessel wall, limiting the possibility of re-treatment at a future date. It is also difficult to conceive of an endovascular approach that would allow us to vary the timing of the radiation therapy (in relation to the PTA) or allow for fractionation of the radiation dose.

External beam radiation therapy with electrons offers an easy answer to most of these problems. It is simple, non-invasive and universally applicable in the community. The dosimetry is very well established and a precise, uniform dose can be delivered to any segment of the vein or graft, without any worry about axial, radial or longitudinal dose inhomogeneity. The timing of the radiation can be varied in relation to the angioplasty in keeping with available information on post PTA cell kinetics. Similarly, dose fractionation is easy and may allow us to deliver a higher dose (if required) for a given level of late side effects. The question of integral dose has been often raised as a problem with external beam therapy. Among the different vascular sites being treated with post-PTA radiation, the dialysis accesses are uniquely suited for external beam therapy because of their very superficial location, usually just beneath the skin. This allows us to use a low electron energy (9 MeV, in most cases). Even if the integral dose is slightly higher, the advantages listed above, including the absence of a radial dose gradient (with consequent "overdosing" of the intima) make this a very attractive approach for access compromise. The only disadvantage is the inability to treat central venous stenosis - endovascular approaches using a gamma-emitter and centering catheters are required for adequate treatment at these sites.

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