Restenosis: A Challenge to Angioplasty

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Fatty deposits clog the coronary arteries blocking blood flow to the heart muscles. This leads to coronary artery diseases. The therapeutic approach is to either provide a by-pass or clear the block by a procedure called angioplasty. However, angioplasty has a high rate of restenosis – renarrowing of the artery in due course. Scientists are looking at various options to prevent restenosis. Application of ionising radiation to the site of angioplasty is one such option.

Anil Deshpande, 67, was rushed to the cardiologist, because of acute chest pain. After giving emergency medication the doctor performed an angiography and found the right coronary artery blocked. It was a case of restenosis. This was the second time in nine months that Deshpande had to visit the cardiologist in an emergency. His case, however, is not unique. One out of every three patients who undergo coronary angioplasty return with restenosis.

What is Stenosis?

The circulatory system serves as transport mechanism to deliver oxygen and nutrients to every part of the body and to remove waste products and carbon dioxide from tissues. The blood flows through a network of arteries, arterioles, capillaries, venules, and veins extending from the top of the head to the tip of the toes. Heart is the central pumping organ of this system. It pumps blood through this extensive network right from the early fetal stage until death.

The heart is made up of a powerful muscle called myocardium, which rhythmically contracts and relaxes, facilitating the pumping action. It needs a regular supply of oxygen and nutrients for its muscles to function. Any interruption to this may spell

disaster. Hence, the heart has its own dedicated blood supply through the coronary arteries. Like with any other system in the body, disease can strike the coronary arteries too. One such life-threatening condition is, what the cardiologists call, coronary artery disease (CAD) or coronary heart disease (CHD).

A common form of CAD is stenosis or the narrowing of the arterial lumen, thereby reducing or totally blocking the blood supply to the heart muscles. As we all know, when we increase our physical activity, the heart beats faster and pumps more blood into circulation. If sufficient blood is not supplied to the heart muscles to meet the increased demand, due to stenosis of the coronary arteries, the heart muscles get strained. This manifests as chest pain, known as angina, which disappears on resting. If the interruption in blood supply is more severe then the heart muscles may die, leading to what is called myocardial infarction, popularly known as heart attack, which can be fatal.

How does Stenosis Occur?

An artery is a tube like structure that carries blood away from the heart. Look at the picture of the heart (*Figure* 1). You can identify the coronary arteries, starting from aorta and branching down to left and right. They get their name because they originate from the top of the heart. Coronary arteries are highly elastic, which enable them to accommodate varying degrees of blood pressure. As with other arteries, a pathologist can identify several layers in the wall of the coronary artery (*Figure* 2). The inner surface of the arterial wall has a smooth lining called the

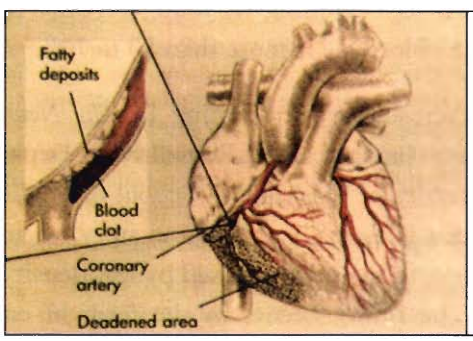

Figure 1(left). Schematic diagram of a heart showing coronary arteries. The inset shows a block in the right artery. Black dots show damaged cardiac muscle.

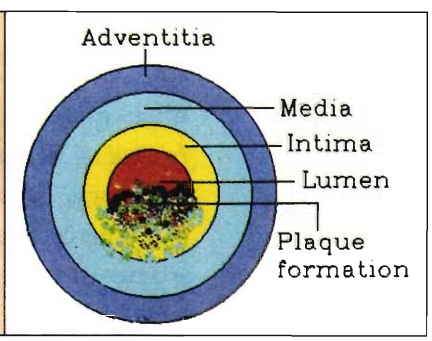

Figure 2(right). A schematic view of coronary artery showing plaque formation.

A sudden critical reduction in blood supply to the myocardium, usually because of plaque rupture and/or thrombosis, leads to acute myocardial infarction.

endothelium, which permits smooth blood flow. This is made up of a layer of endothelial cells. The endothelium with subendothelial connective tissue forms the innermost layer of the arterial wall called *tunica intima*. This is surrounded by a membrane-like layer of elastic tissue. Immediately below this membrane is the *tunica media* composed of smooth muscle cells and elastic tissue. The outermost layer of the arterial wall, *tunica adventitia,* consists mostly of loose collagen fibers. The outer layers provide structural support to the artery.

Stenosis begins in the intima with the deposition of fatty debris from blood. Smooth muscle cells from the internal elastic membrane and media proliferate into intima. Collagen and elastin produced from these cells accumulate resulting in a fibrous plaque. Platelets and cholesterol soon begin to adhere to the plaque. As the process continues, cholesterol rich material, particularly the low-density lipids, and necrotic cells, accumulating in the plaque cause it to encroach upon the arterial lumen (*Figure 2*). Eventually, the plaque calcifies and hardens. The narrowed lumen of the artery does not permit adequate blood flow causing that portion of the myocardium to become ischemic. An advanced plaque may rupture or platelets may aggregate at the site to produce an intravascular blood clot or thrombus. A sudden critical reduction in blood supply to the myocardium, usually because of plaque rupture and/or thrombosis, leads to acute myocardial infarction.

The process of plaque formation is called atherosclerosis. It does not occur overnight. Cardiologists are of the opinion that it is a slow process with its beginning in younger years. Its effects manifest when the blockade is more than 50 to 70%.

What causes atherosclerosis? Writing in *The New England Journal of Medicine* (January 1999), Russell Ross, Department of Pathology, University of Washington School of Medicine, says that atherosclerosis is basically an inflammatory reaction of the arteries in response to the injury caused by low density lipoproteins (LDL). The injury occurs in the form of endothelial

dysfunction and its permeability to blood constituents. If the source of injury is not removed a complex series of cellular and molecular events as described above take place resulting in atherosclerosis. In addition to LDL other risk factors for atherosclerosis are high blood pressure, cigarette smoking, sedentary lifestyle and certain genetic factors.

Diagnosis and Treatment of Stenosis

Unlike bone, the arteries, the blood, and the atherosclerotic plaque are transparent to X-rays and do not show up on ordinary X-ray film. In order to image the arteries, cardiologists trick the system in a procedure called angiography. They first make an incision in the femoral or brachial artery and gently push a catheter all the way to the coronary artery. Then, they inject an iodine compound opaque to X-rays and follow it up, under X-ray fluoroscopy, as it moves down the artery. Wherever the flow is blocked, it clearly shows up as a discontinuity or narrowness in the dark image cast by the iodine compound (*Figure* 3). More recently, a new device called intravascular ultrasound (IVUS) has been developed. IVUS is capable of imaging the plaque and its distribution without X-rays. Another method called thallium scintigraphy, which utilizes radioactive thallium, measures the perfusion of blood through the cardiac muscle to determine the extent of damage.

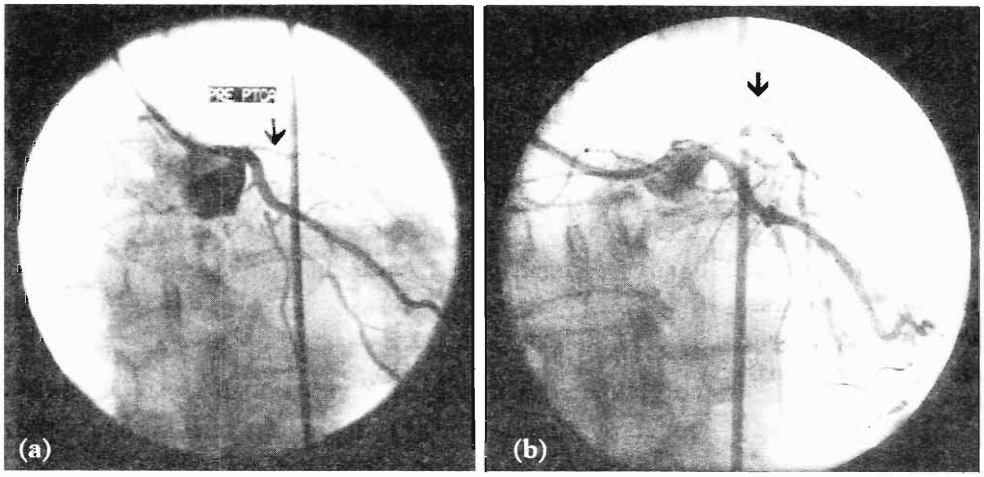

Figure 3. Angiogram of a coronary artery before and after angioplasty (arrows). (a) Narrowness in the artery shows a block. (b) Block is cleared after balloon angioplasty. Note that the artery has become wide.

One of the main reasons for early restenosis is the elastic property of the arterial wall.

For treatment of the stenosed artery, a by-pass can be provided for the blood flow. However, by-pass surgery is a high-risk procedure and expensive. Alternatively, over the past thirty years, cardiologists have perfected a safer and less expensive method called percutaneous transluminal coronary angioplasty (PTCA). In PTCA, after angiography, a balloon, in its collapsed form, attached to a catheter, is introduced into the artery and pushed carefully to the stenosed portion. Once in position, it can be inflated from outside. The expanding balloon exerts radial pressure over the plaque compressing and breaking it into pieces, thus clearing the lumen. Interventional cardiologists prefer PTCA to by-pass surgery, unless contraindicated.

Restenosis

Unfortunately, the benefits of PTCA do not seem to be as endurable as desired. One of the main problems of PTCA is restenosis or renarrowing of the arterial lumen occurring either immediately (early restenosis) or over a period of months (late restenosis). One of the main reasons for early restenosis is the elastic property of the arterial wall. The artery may collapse when the balloon pressure is released. To prevent this, a metallic stent is inserted in some cases at the site of angioplasty. A stent is an expandable cage made of titanium or stainless steel wires. It is inserted through a catheter and expanded from outside by a balloon. Stents resist the elastic recoil of the artery by providing a scaffold and minimize the loss of lumen (*Figure* 4). This improves the short-term results of PTCA. However, they do not appear to eliminate late restenosis. Some cardiologists are of the opinion that stents may actually promote restenosis. It is common to see in any large cardiac center, 35 to 40% of the patients undergoing PTCA come back within six months with the problem of restenosis. The present management of restenosis is repeat angioplasty or by-pass surgery. In fact, because of restenosis, most of the cost benefit of PTCA vis-a-vis by-pass surgery in the first place appears to be lost. Prevention of restenosis after a successful angioplasty remains one of the major challenges of interventional cardiology.

Figure 4. A metallic stent placed in the artery after angioplasty. It provides scaffolding support and prevents early restenosis.

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What causes late restenosis? Recent research has revealed that the cause of late restenosis is, again, the natural wound healing reaction in the wall of the artery. The expanding balloon applies a pressure as high as 20 atmosphere for a period lasting from a few seconds to minutes. It not only crushes the plaque but also disrupts the intima and sometimes even the media of the arterial wall. In response to this wound, inflammatory cells – monocytes, macrophages, lymphocytes, etc. infiltrate the site of injury. Platelets, activated within the intravascular blood clot, release cytokines such as platelet-derived growth factor (PDGF). PDGF stimulates the growth of smooth muscle cells and myofibroblasts. They migrate into intima resulting in what is known as neointimal proliferation. Within weeks to months, the healing site resembles a fibrous plaque, which is the beginning of restenosis. In most patients, the lumen enlarging effect of angioplasty outweighs the risk of restenosis. However, in nearly 40% of the patients this is not so. Neointimal growth extends into the lumen compromising blood flow and oxygen delivery. Researchers are looking at various ways of preventing restenosis.

Drugs such as beta-blockers, calcium channel blockers, nitrates, oxygenated fluorocarbons, following angioplasty help maintain the lumen. Animal experiments have also shown that applying the pressure in a protracted manner (15-min *vs* 1-min) can also somewhat reduce the rate of restenosis. Other researchers have tried more aggressive methods like tissue cutting (atherectomy), abrading (rotoblator) or vaporizing the plaques by lasers. These techniques can be applied if the artery is too narrow for balloon insertion or the plaque is too hard due to calcification. However, they are also associated with the high risk of perforating the arterial wall and do not protect against restenosis. More recently, nuclear radiations are being considered as an effective tool to inhibit restenosis, since they act by an entirely different mechanism.

Vascular Brachytherapy

Oncologists and physicists involved in the treatment of malignant and non-malignant tumors have known for decades that

nuclear radiatons can readily knock out rapidly dividing cells. They do so by causing extensive and irreparable damage to the DNA in the cells. It was only logical to extend this approach to the vascular smooth muscle cells, which are at the root of restenosis. First animal experiments, particularly with pigs (for they have arteries similar in size to those of humans), were conducted to test the idea. In these experiments, balloon overstretch injury was caused in one or more arteries of the animals and then one set irradiated to graded doses of radiation. The animals were sacrificed at various intervals of time (weeks to months) and their arteries examined for the efficacy of radiation to inhibit restenosis. The irradiated artery had maintained the lumen, while the control artery had developed stenosis (*Figure* 5). The immunosuppressive action of radiation prevented the initial inflammatory response. In addition, radiation also inactivated the proliferating smooth muscle cells and myofibroblasts, inhibiting neointimal formation. After careful analysis of such experiments, the first human trial was conducted by cardiologists at Caracas, Venezuela in 1994. This opened a floodgate of clinical trials in Europe and North America.

The trickiest part of the business is the delivery of radiation to the site, which is inaccessible, fragile, and only a few millimeters in diameter. The dose has to be precise. Too high a radiation dose will cause unacceptable damage to the artery and the heart muscle. Too low a dose will be ineffective. Brachytherapy is a system employed by oncologists to treat cancers in body cavities

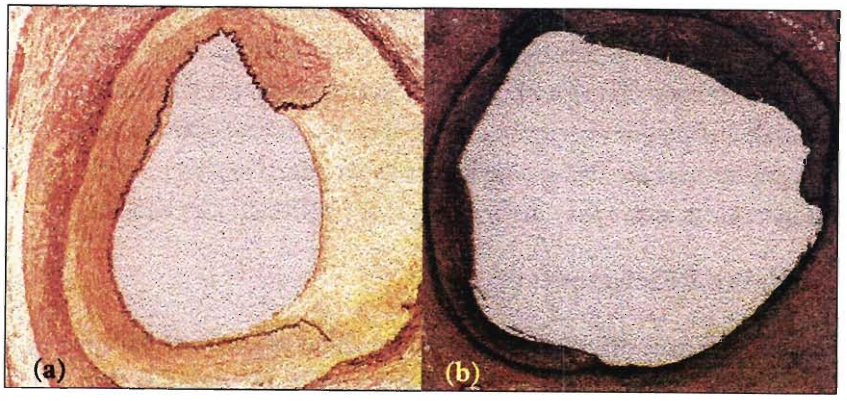

Figure 5. Micrographs of (a) control and (b) 14 Gray irradiated injured coronary arteries of miniature pigs killed two weeks after balloon stretch injury (Gray is a unit of radiation dose). (Picture courtesy: Nucletron).

such as cervix. In this system, the radiation source is placed close to the tumor for irradiation. This system has been modified to meet the needs of the cardiologist. Appropriately, it is called vascular brachytherapy. The most popular vascular brachytherapy systems are either catheter based or employ radioactive stents. In catheter based systems, high intensity radioactive sources, in the form of a thin wire or tiny pellets attached to the end of a specially designed catheter, are introduced to the site of angioplasty by a remote operating system. The irradiation may last for 3-5 minutes after which the source is retracted (*Figure* 6). Alternatively, a stent implanted with a small amount of radioactive material is placed permanently at the site of angioplasty. In addition to providing the scaffolding support, it also delivers the radiation dose in a measured way to knock out the proliferating smooth muscle cells. Prominent among the radiation sources are the gamma-ray emitting Iridium-192 wires or beta-ray emitting Strontium-90 pellets generally used in catheter based devices,

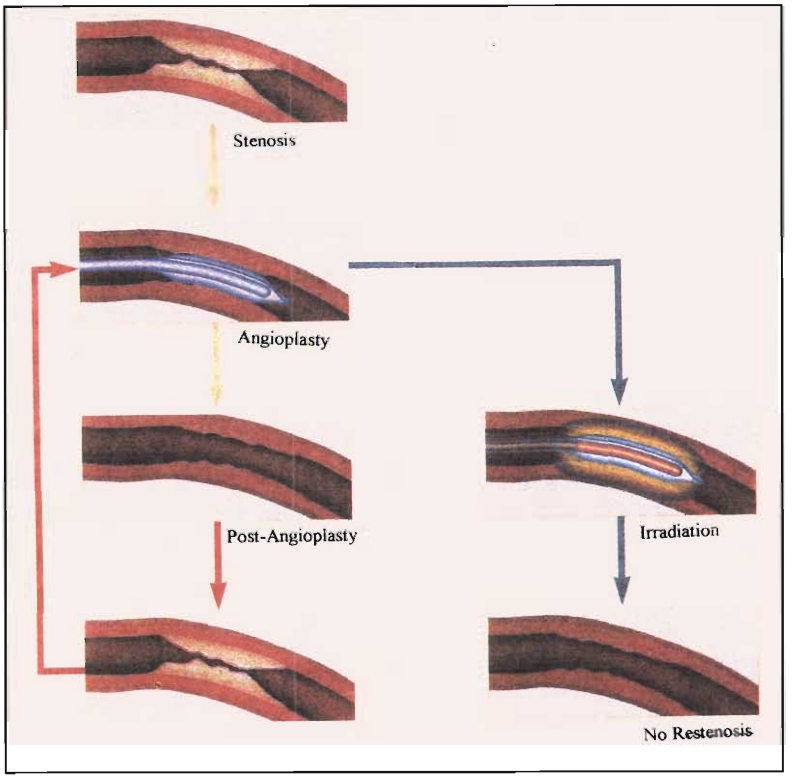

Figure 6. Steps in vascular brachytherapy in which a tiny radioactive source attached to the end of a catheter irradiates the smooth muscle cells to prevent restenosis after angioplasty. (Picture courtesy: Nucletron)

Suggested Reading

[1] Intravascular Brachytherapy Physics: Report of the AAPM Radiation Therapy Committee Task Group, No. 6, *Med. Phys.*, 26(2), pp 119-150, February 1999.

[2] Philip Rubin, Arvind Soni, and Jacqueline P Williams, Molecular and Cellular Biologic Basis for the Radiation Treatment of Benign Proliferative Diseases, *Seminars in Radiation Oncology*, Vol. 9, No.2, pp 203-214, April 1999.

[3] Russell Ross, Atherosclerosis – An Inflammatory Disease, *New England Journal of Medicine*, Vol. 340, No.2, pp 115-126, 1999.

[4] Vascular Radiation '99 - International Conference on Intracoronary Radiotherapy, Hyderabad, 14-15, August 1999.

and beta-ray emitting Phosphorus-32 used in stents. A large number of clinical trials around the world, using both systems of dose delivery, are showing very encouraging results. A review published by the American Association for Physicists in Medicine in 1999, reports that restenosis may drop from roughly 35 to 40% to well below 10% if radiation is delivered to the obstruction site during or after angioplasty.

Restenosis is not a feature of only the coronary arteries. Arteries supplying blood to brain and extremities may also be blocked leading to ischemia or infarction of brain, limbs, etc. Nuclear radiations have been found useful in reducing restenosis in these arteries also.

Indian Trials

In August 1999, a group of interventional cardiologists from India and USA met for two days in the Apollo Hospital at Hyderabad. The American team presented results of nearly 30 on-going clinical trials involving more than 5000 patients, which showed that the rate of restenosis could be cut down by half to one third by irradiation (*Box* 1). These clinical trials have been given curious acronyms like *inhibit, cure, radiant, prevent, artistic, scripps*, reflecting both the system of irradiation and the goal of the clinical trials. The occasion was to initiate a multicentric study involving four major hospitals in Hyderabad – Apollo, Care, MediCiti, and Bibi Cancer Center along with Long Beach Memorial Medical Center at California, USA. Forty-two patients have enrolled in the Indian study. In another effort, the Bhabha Atomic Research Center, Bombay, supplies stents coated with radioactivity. Nanavathi Hospital in Bombay was the first in India to try this novel approach to manage restenosis. A number of other clinics in Bombay, Delhi, and Hyderabad are now participating in a multicentric study using radioactive stents.

The results of all these studies are eagerly awaited.

Notwithstanding the encouraging clinical trials, there are a

Box 1. Incidence of Coronary Artery Disease in the Indian Population

It is estimated that about 13 lakh cases of coronary artery disease (CAD) occur every year in India and account for 10% of deaths. While the incidence of CAD in developed countries is coming down in the past two decades due to increased awareness and changing lifestyle, the opposite has been true in the case of developing countries. This is attributed to increased life expectancy, changing to affluence-oriented lifestyle and improved diagnosis. By the year 2015, the incident rate in India is expected to double and account for one out of every four heart patients in the world. In fact two studies, one each conducted in UK and USA on immigrant Indians, show that, despite being vegetarians, they have a higher incidence rate of coronary artery disease than the local white population. The UK study was conducted by Dr. Jespal Kooner of the Imperial College, School of Medicine, London. It was found that the endothelial cells lining the arteries expand and contract, in response to blood flow, much less in a group of Punjabis than in the native whites. In the US study, one of the investigators, Dr. Michael Miller, Director of the Center for Preventive Cardiology, University of Maryland, has suggested that a genetic factor causing an impaired metabolism of triglycerides, a type of fat circulating in blood, is responsible for the increased susceptibility to plaque formation.

number of issues, which have to be resolved before nuclear radiations can be accepted as an effective tool to fight restenosis. These include the choice of radiation – between the penetrating gamma radiation or beta radiation with shallow penetration; the type of device – catheter based or stent; the timing of irradiation; the quantity of radiation; and even the target cells which have to be knocked out. Researchers are confident of finding answers to all these questions.

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I do not know what I may appear to the world, but to myself I seem to have been only a boy playing on the sea-shore, and diverting myself in now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me.

Newton