Medical Biomaterials
Prof. Mukesh Doble
Department of Biotechnology
Indian Institute of Technology, Madras

Lecture - 39
Cardiovascular/Occular

Hello everyone welcome to the course on medical biomaterials. We will talk about some of the biomaterials used in cardiovascular and occular area. We have been looking at quite lot of biomaterial used in orthopedic as well as in dental. I thought another big area is cardiovascular and of course, biomaterial used in eye. So, we will briefly touch upon the metals, the ceramics, the polymers used in this area. So, cardiovascular, they interact with the heart blood and blood vessels. So, they have different functions. So, the failure modes could be mechanical failure.

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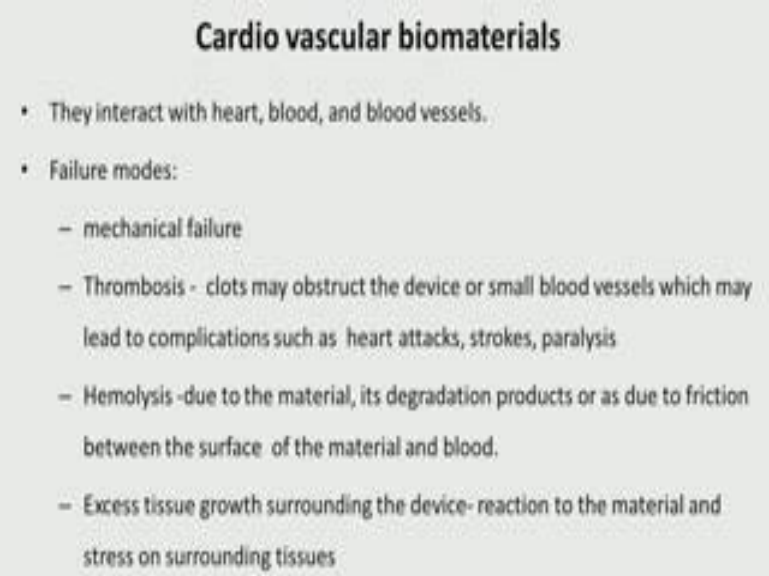

For example, if you have the left ventricle assist device or a diaphragm valve which opens closes or a pump heart, pump they can have mechanical failure. Thrombosis blood clotting can happen because of the device and then blood vessels may get blocked. So; which can lead to, stokes, paralysis, attacks, heart attacks; hemolysis because the material surface maybe a little bit rough. So, it may activate your platelets, the red blood corpuscles, though they can start getting activated because of friction and then excess

tissue growth surrounding this device. So, the tissues may start growing and which may lead to stress between the material and tissues surrounding.

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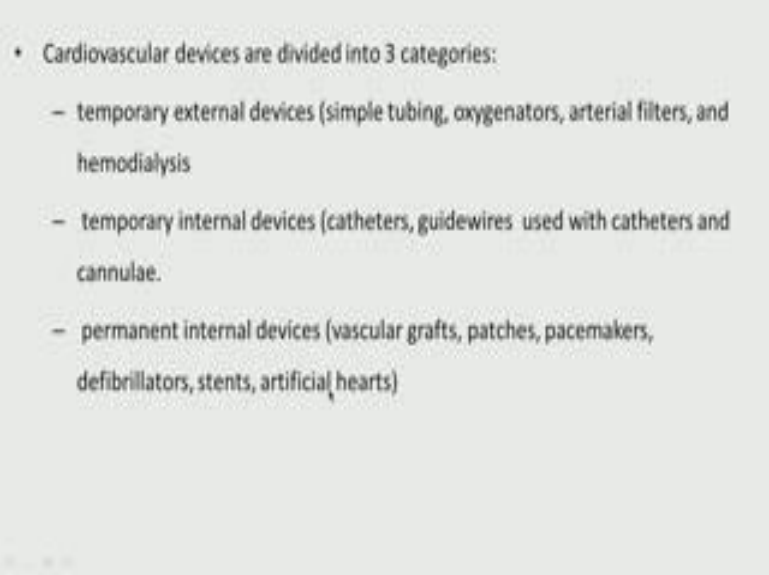

So, these are divided in to three categories, temporary devices; that means, like a tubing, simple tubings, oxygenators, arterial filters, hemodialysis temporary internal devices. The previous one was temporary external devices; internal devices like your catheters, guidewires used for catheters, cannulae and if any other angioplasty related activities done there could be many temporary devices.

Then permanent devices vascular grafts, patches, pacemakers, defibrillators, stents, artificial hearts, all these you know valves and so on actually.

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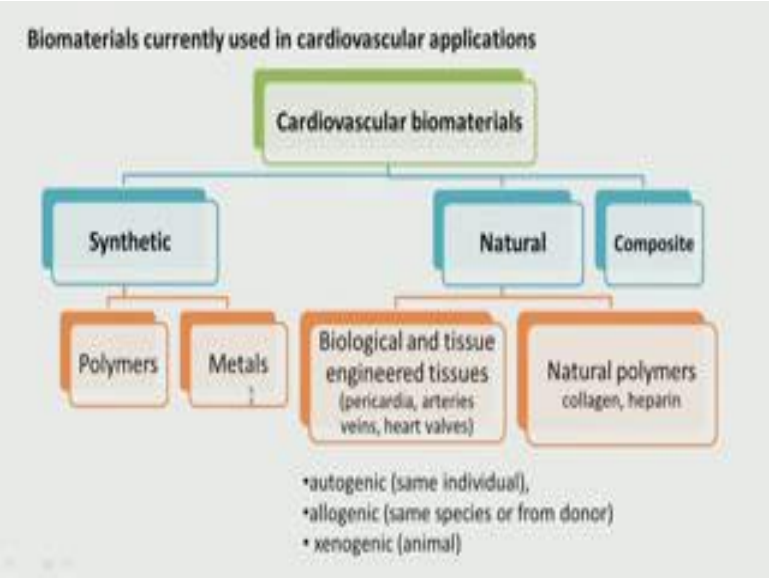

So, we can add synthetic materials, we can have natural or composite synthetic could be polymers of course, metals, natural could be biological and tissue engineered like pericardia, arteries, veins, natural polymers like collagen, heparin. So, the biological tissues could be autogenic from the individual allogenic from the same species or from a donor xenogenic it could be from animal. So, each has its advantages and disadvantages.

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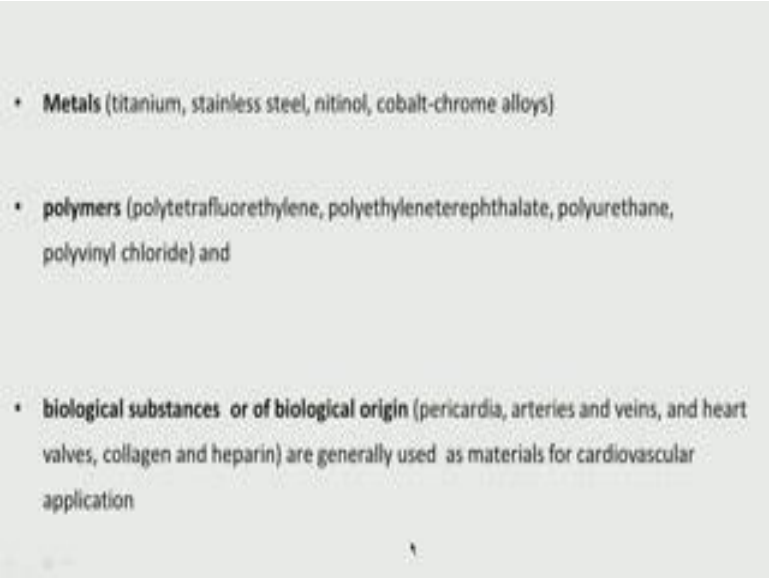

So, titanium, stainless steel, nickel, titanium, combination, cobalt, chrome, all these are used polymers PTFE, PET, polyurethane, polyvinyl, chloride and biological could be

pericardia, arteries, veins, heart valves, collagen, used as material for cardiovascular applications.

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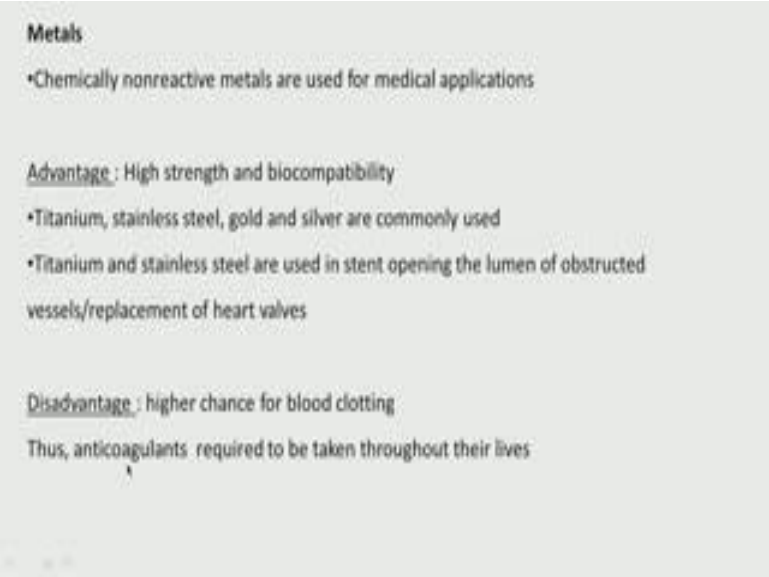

Materials of course, are nonreactive. So, good strength and biocompatibility, titanium, stainless steel, gold, silver, they are used quite a lot in lead wires of course, disadvantages; there could be blood clotting. So, they have to be coated with some anticoagulant material or the patients have to for lifelong take medication to prevent coagulation of the blood that is a problem with metal (Refer Time: 03:47).

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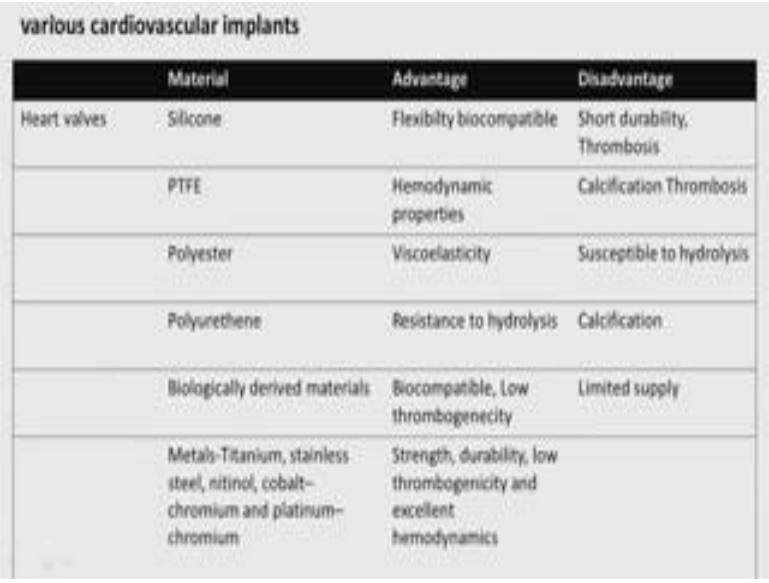

So, various cardiovascular implant heart valve, silicone, PTFE, polyester, polyurethane or biologically derived material. So, all these are used.

So, advantages disadvantages. So, like some of these are very good. PTFE has good hemodynamic property, polyester is viscoelastic, polyurethane resistance to hydrolysis, but they could have calcification or thrombosis. Biologically derived material of course, is very good, but then they are limited supplies tends. If you take metals titanium, stainless steel, nitinol, all these are used in heart valves.

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	Material used	Advantage	Disadvantage
Vascular grafts	ePTFE (GORETEX)	Low thrombogenecity, high strength, easy handling	negative immune response
	PET	Tissue ingrowth, biocompatibility, high patency	
	Biologically derived materials	Biocompatible, Low thrombogenecity	Limited supply
Stents	Metals- Titanium, stainless steel, nitinol, cobalt–chromium and platinum–chromium	Strength, durability, low thrombogenicity and excellent hemodynamics	
	Composites –Carbon fibre based, Epoxy	Strength, durability	
Pacemaker leads	PU	Strength, elasticity, transparency, resists infection and improved handling	
	Metals- Ti, SS , Nitinol, Co–Cr, Pt-Cr	Strength, durabile, low thrombogenicity , hemodynamics	

Let us look at vascular grafts, PTFE is used low thrombosis, high strength, of course, disadvantages immune response, PET, tissue ingrowth, biocompatibility is a problem. Biologically derived material they are very good, but limited supplies tends. Now lot of metals are used, originally titanium was used, stainless steel, nitinol, cobalt, chromium, and then again coated stents, drug eluting stents. They are very good durable, lower thrombogenicity, excellent hemodynamics. Composites carbon, fiber, based Epoxy, they are also very good strength. Pacemaker leads polyurethane, metals like titanium, stainless steel, cobalt, chromium, platinum, chromium and so on actually.

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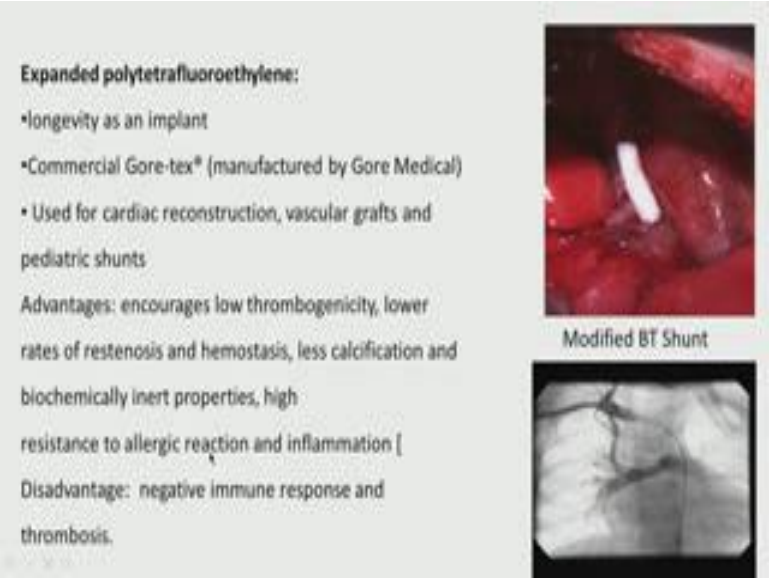

Let us look at EPTFE; that is expanded polytetrafluoroethylene, it is long, longevity is very good. There is a manufacturer called Gore tex. This is a picture of this is used as a shunt. It is connecting different parts especially aorta, this is used for cardiac reconstruction, vascular grafts and pediatric shunts, these are all pediatric.

So, this is made up of PTFE, this may be about 2, 2.5 MM diameter. Advantages; it encourages low thrombogenicity, lower rates of restenosis, hemostasis, less calcification and biochemical inert. It is also resistant to allergic and inflammation. Disadvantage; negative immune response and thrombosis.

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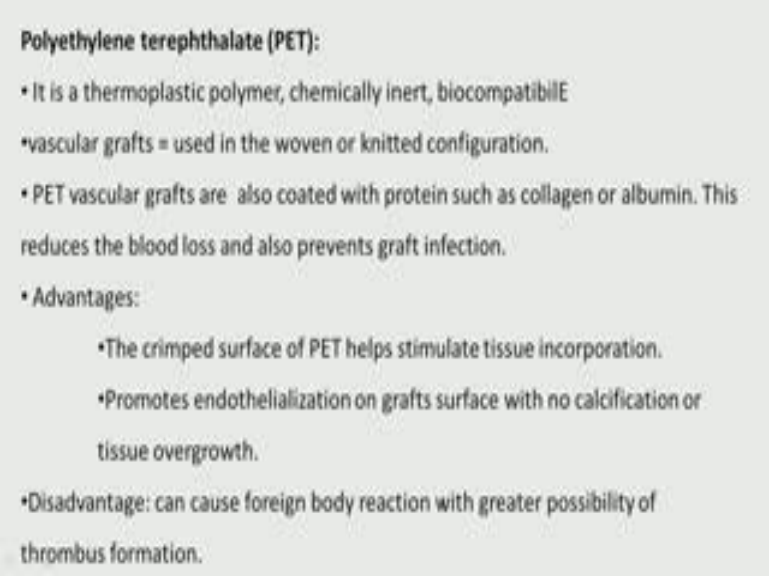

PET; it is chemically inert, biocompatible. It is used in vascular grafts, large diameter vascular grafts. It is woven; you can quote it with protein or collagen albumin and so on to reduce blood loss. The crimp surface of PET helps stimulate tissue incorporation, promotes endothelialization on graft surface. No calcification of course, it can create foreign body reaction with greater possibility of thrombosis formation.

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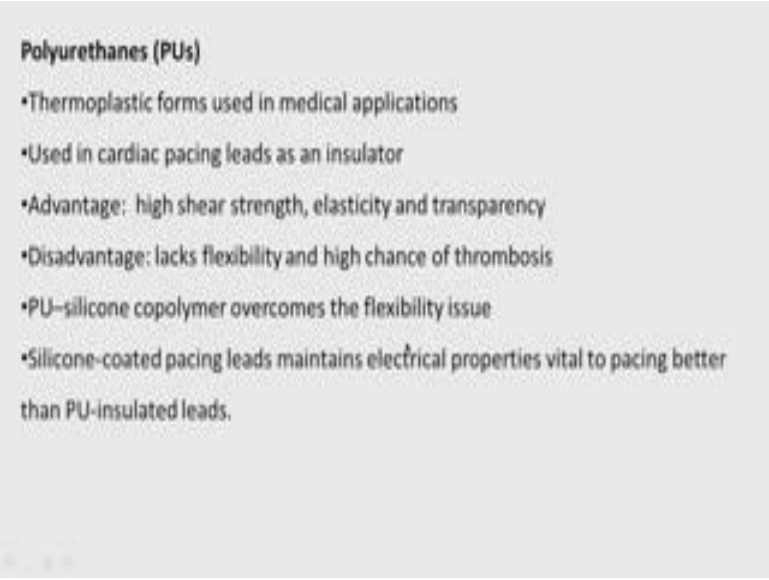

Polyurethanes; it is thermoplastics used quite a lot in medical applications, used in cardiac pacing leads; it is used in other areas also. High shear strength, elasticity,

transparency, lacks flexibility and high chance of thrombosis. PU silicone copolymers are used in some of these to improve the flexibility. Silicone coating, pacing leads, maintain electrical properties, for better pacing than PU alone.

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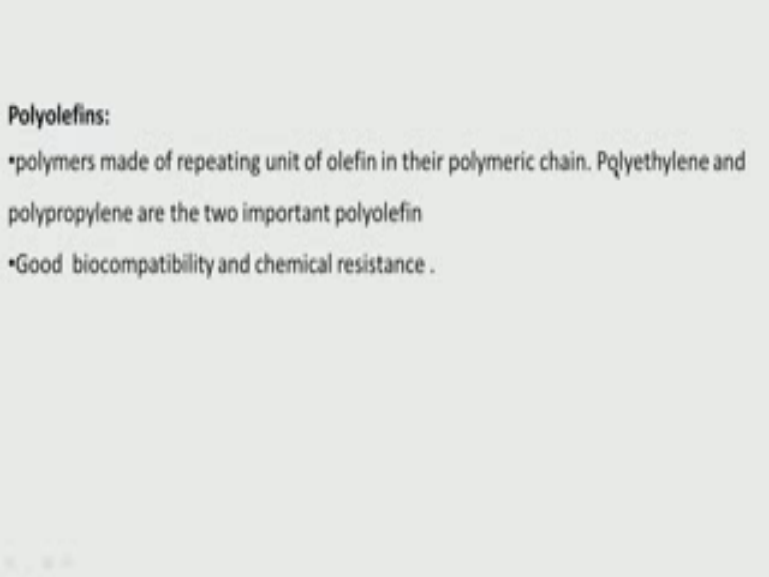

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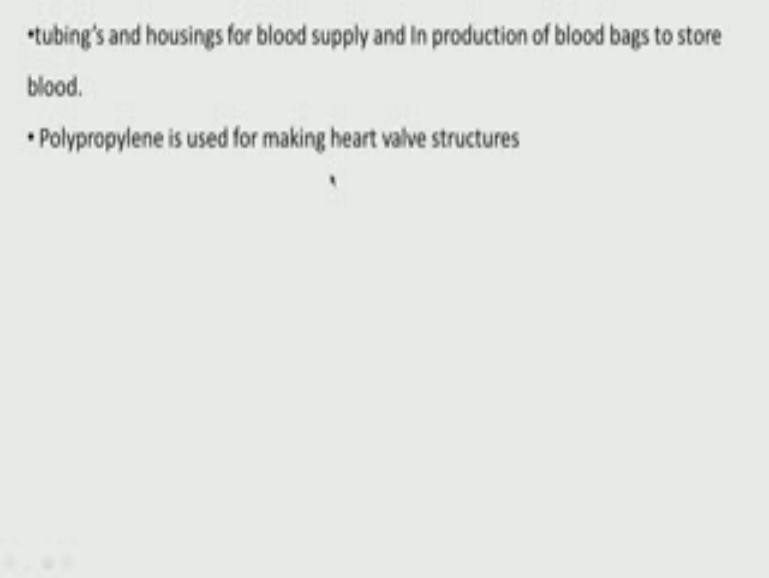

Polyolefins; polyolefins they have good biocompatibility and chemical resistance especially polyethylene and polypropylene. So, they are used as tubings, housing for blood supply production of blood bags, to store blood. Polypropylene is used for making heart valve, structures and so on actually.

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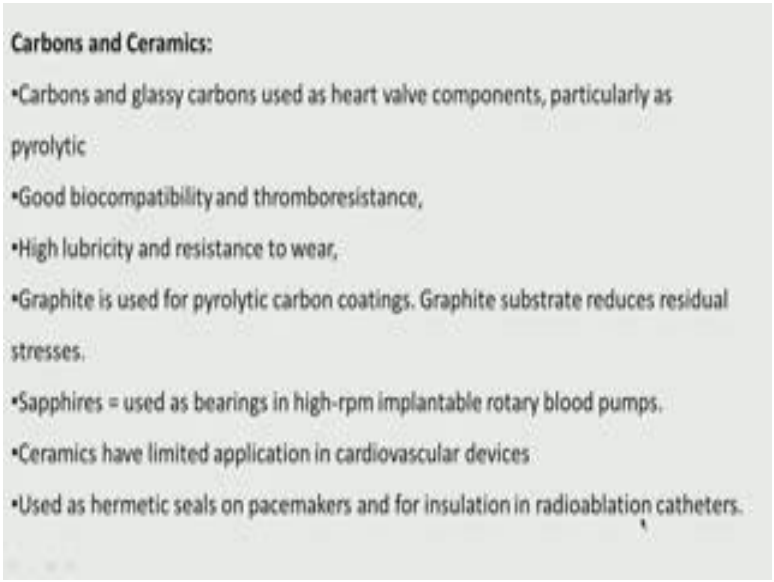

Carbon and ceramics; carbon, glassy carbon they are used in heart valve components, pyrolytic. Good biocompatibility and thromboresistace, high lubricity resistance to wear.

Graphite is used pyrolytic carbon coatings and sapphire used as bearings in high rpm implanted rotary blood pumps. So, they have blood pumps for patients whose heart is very weak and the heart is not able to pump. Then of course, you have high rpm sapphires are used there as bearings. Ceramics limited applications in cardiovascular devices. They are of course, used in hermetic seals on pacemakers, insulation and so on actually.

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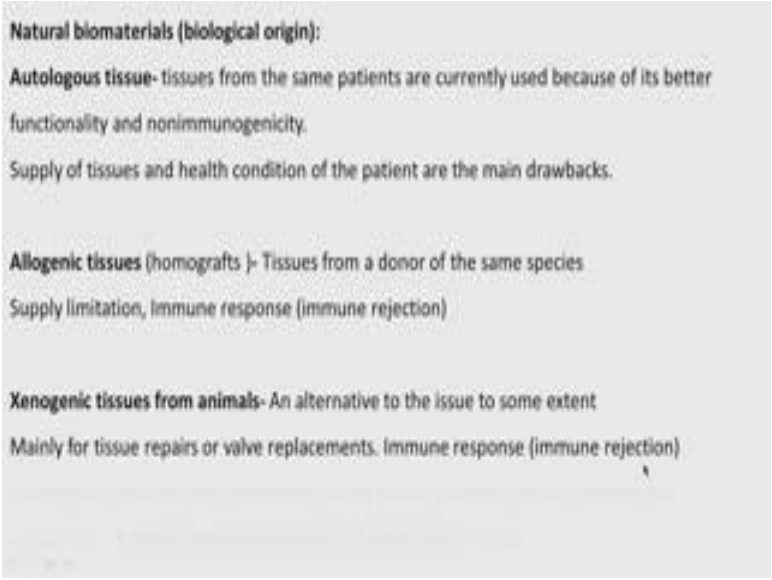

Natural biomaterials; they are natural biological in origin like autologous tissue, that is tissues from the same patient you make use of it. So, there is no immunogenicity problem, rejection problems are there, but of course, the supply is a big problem. Allogenic tissue homografts it is tissues from a donor supply again limitations. There could be immune rejection. Xenogeneic this could be from animals. This is an alternate, but there could be transmission of a disease, but there is a lot of interest nowadays in using animal tissues, especially for repair of valves replacements and so on. Of course, there also you can have immune rejection as well as disease getting transmitted. Bovine, porcine, equine tissues, are generally used in cardiovascular applications.

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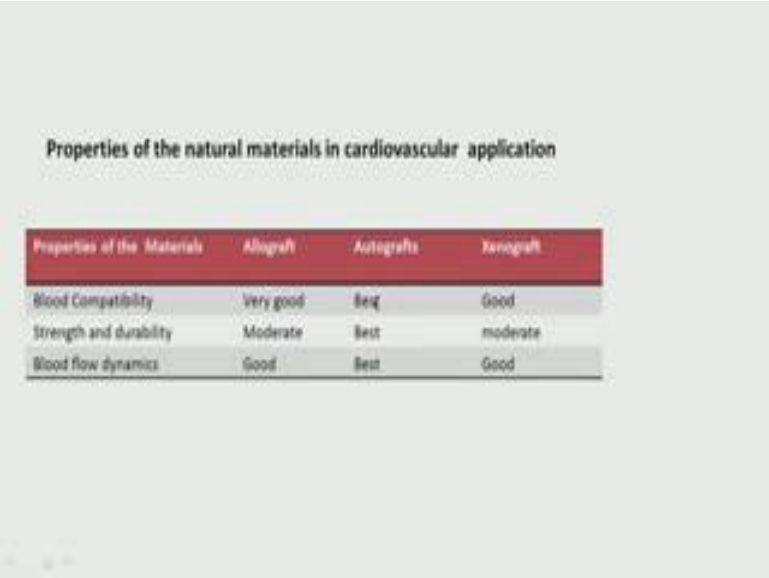

So, some of these blood compatibility of allograft of course, though they are donors own. So, very good autografts, best strength and durability, moderate, moderate, blood flow dynamics again this reasonably good.

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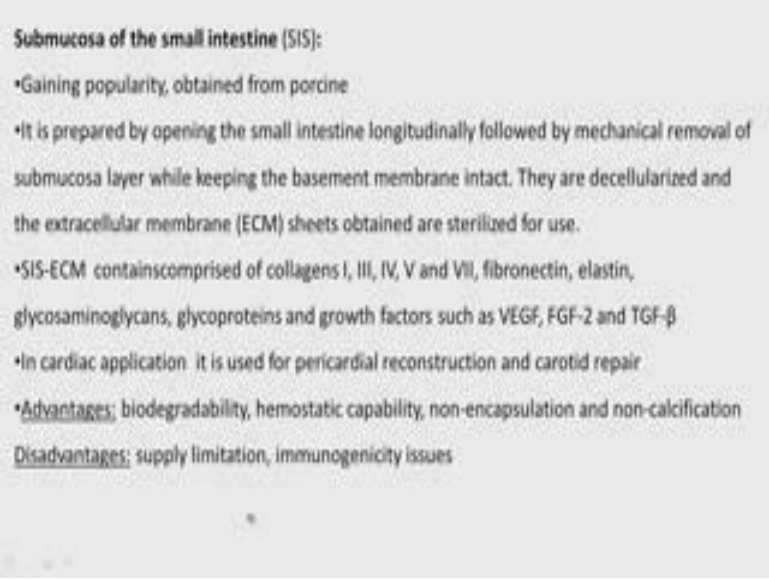

Submucosa of the small intestine, there is some interest in that. It is gaining popularity from porcine; it is prepared by opening the small intestine longitudinally followed by mechanical removal of the submucosa layer while keeping the basement membrane intact.

Then you cell, decellularized the extracellular membrane sheets and which you sterilize it actually. So, this submucosa of the small intestine ECM; extra cellular membrane, it contains collagen 1, 3, 4, 5, 7, fibronectin, elastin and quite a lot of growth factors. So, they say it is extremely good for cardiac applications, for pericardial reconstruction. So, very good biodegradability, hemostatic capability, non encapsulation, non calcification, of course, again the disadvantage is supply limitation immunogeneticity issues, so maybe transferring disease.

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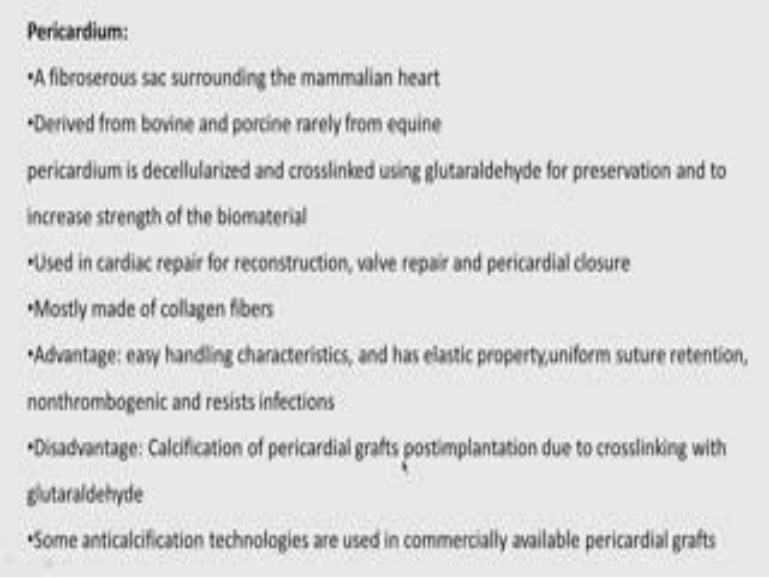

Pericardium a fibrous sac surrounding the mammalian heart, so you can harvest it from bovine or porcine and then it is decellularized and cross linked using glutaraldehyde for increasing the strength as well as preserving. And then this can be used for cardiac repair, reconstruction, valve repair and pericardial closures. This is mostly made up of collagen fibers. So, easy handling characteristics, it is elastic, uniform suture retention, nonthrombogenic, resists infection. Big problem is calcification of pericardial grafts after implantation due to cross linking with glutaraldehyde. Some anti calcification techniques are also there commercially available.

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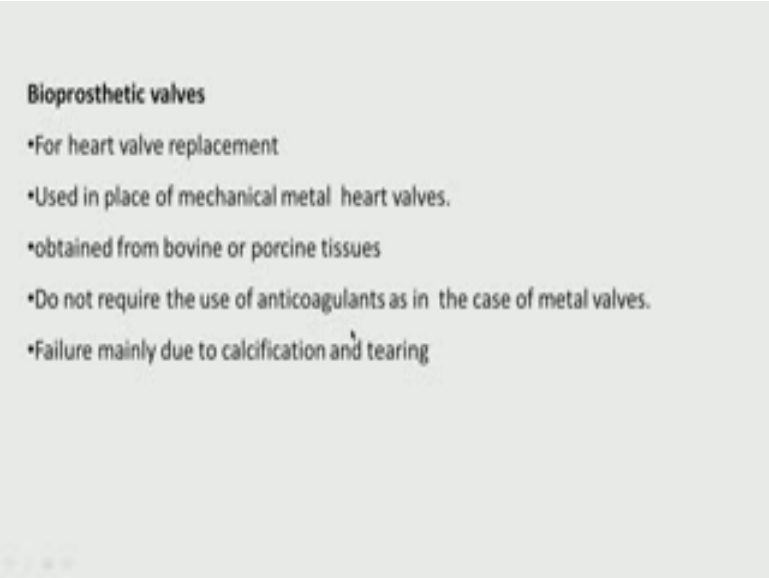

Look at bio prosthetic valve; these are for replacement of heart valves in used in place of mechanical metal heart valves is again obtained from bovine or porcine. So, it does not require anticoagulants, if you use metal you may require that. Failure mainly due to calcification and tearing lacks the strength. So, it can tear or calcify.

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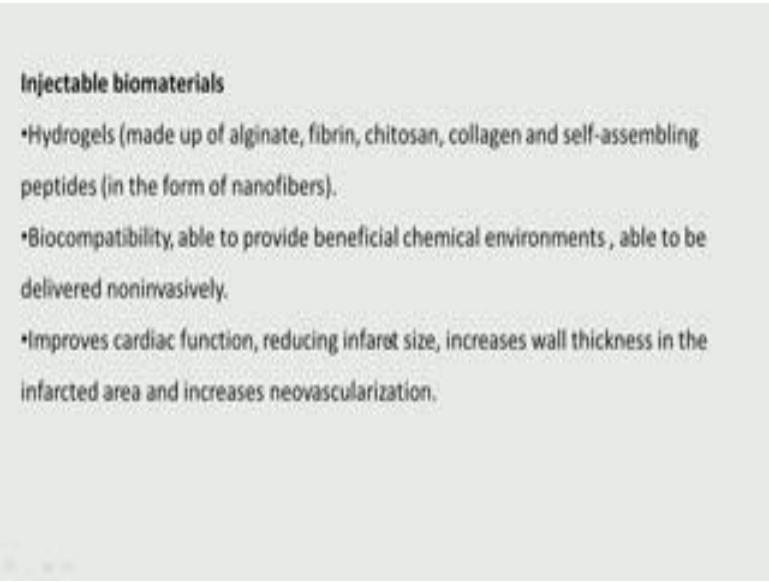

Injectable biomaterials like hydrogels made up of alginate, fibrin, chitosan. So, they are very good biocompatible, good chemical environment, able to deliver, it can improve

cardiac function, reduce infarct size, increase wall thickness in the infarcted area. So, if there is a wound or infection, it can cure it.

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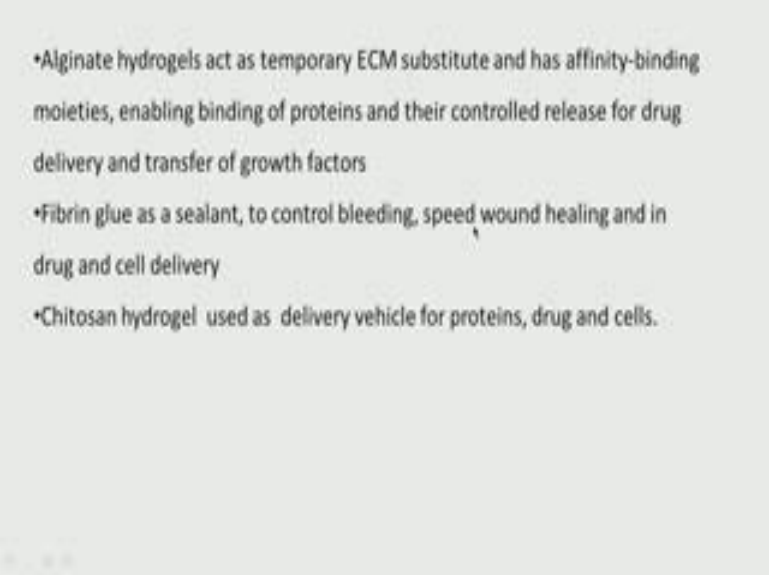

Alginate hydrogels they are used temporary ECM substitutes and has affinity binding moieties, enabling binding of proteins. So, they can be used for control drug release. Fibrin glue as a sealant; suppose there is a bleeding and as you know fibrin is a blood clot. So, it can be used for preventing bleeding, speed up wound healing and in drug and cell delivery. Chitosan hydrogels for delivery of proteins drugs and cells.

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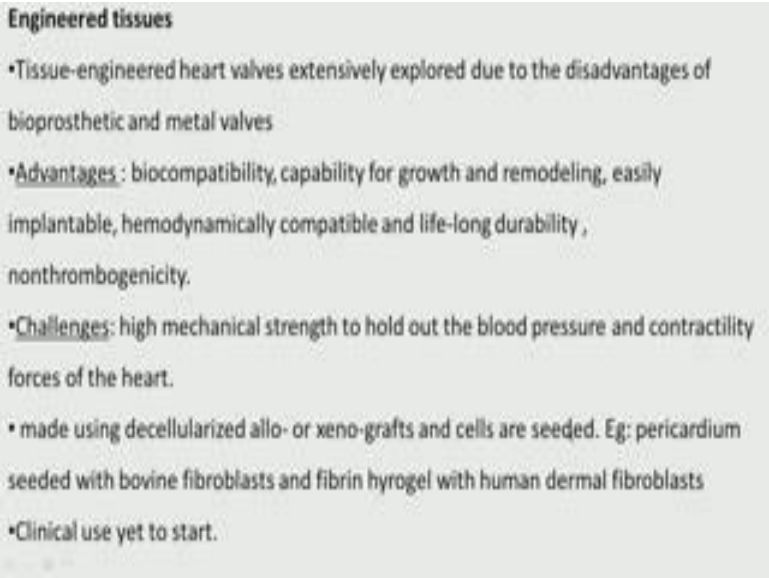

Of course engineered tissues, these are tissue engineered heart valves still they are under research and they are being explored, but still they are not come in to market, they as a replacement for bioprosthetic or metal valves actually. Engineered of course, they will be biocompatible; we can grow any type of cells on that, long duration and so on. Challenges are high mechanical strength to hold the blood pressure and contractive forces there. So, basically you can make it using decellularized allo or xeno grafts and cells are then seeded on top of that. That is the way in which it is made. As I said it is clinically not been started.

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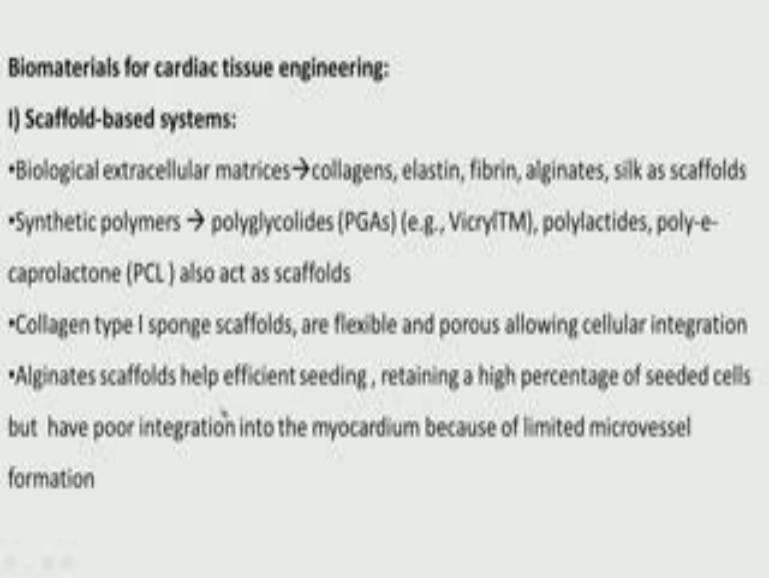

So, what are the biomaterials for cardiac tissue in a scaffold based materials like collagen, elastin, fibrin, alginates, silk as scaffolds, synthetic polymers like polyglycolic, PGA, polylactides, polycaprolactone, collagen type one sponge scaffolds, flexible and porous allowing cellular integration. Alginate scaffolds; they helps efficient seeding, retaining high percentage of seeding cells and so on.

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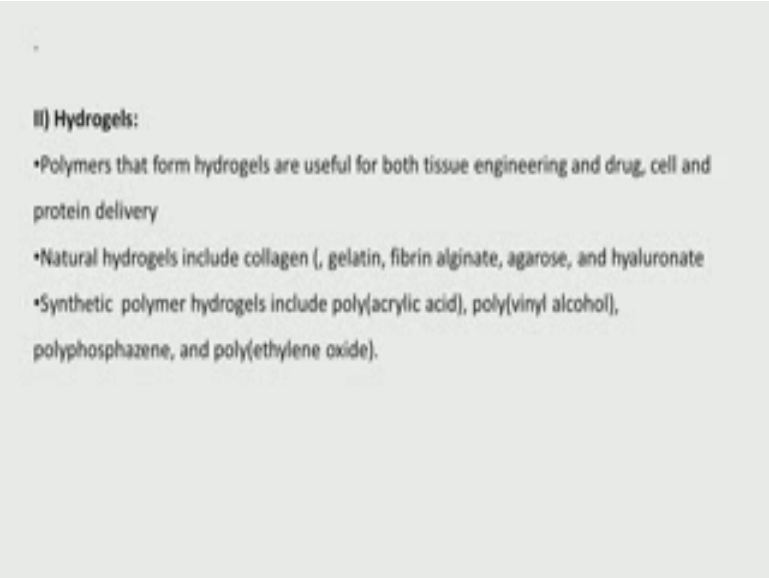

Hydrogels we looked at scaffold based materials hydrogels; that means, they use polymers which form hydrogels, natural hydrogels we talked quite a lot about hydrogels. I will not spend much time like gelatin, fibrin, alginate, agarose, hyaluronate, synthetic polymer based poly acrylic acid, polyvinyl alcohol and so on. So, hydrogel is another approach or decellularized tissues.

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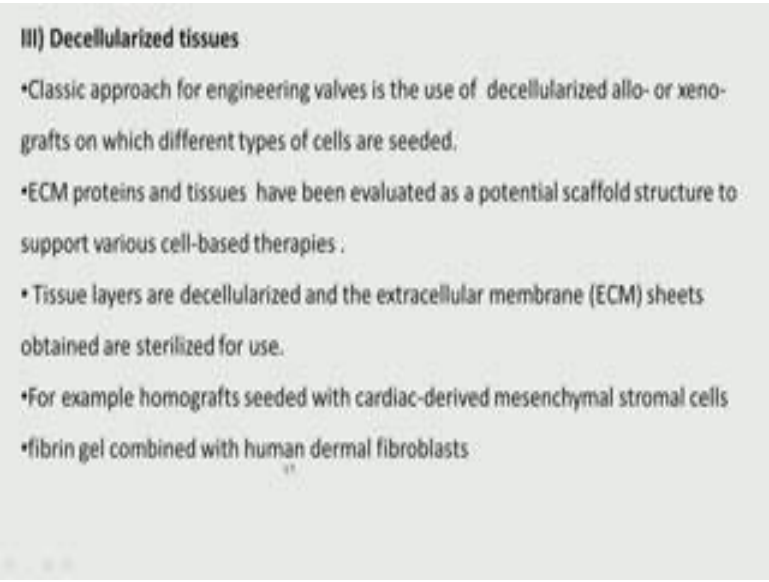

So, you take the tissues allo or xeno and then you decellularized and then cells are seeded. ECM proteins and tissues have been evaluated as a potential scaffold to support

various tissue. Homografts seeded with cardiac derived mesenchymal stromal cells, fibrin gel combined with human dermal fibroblasts; so different types.

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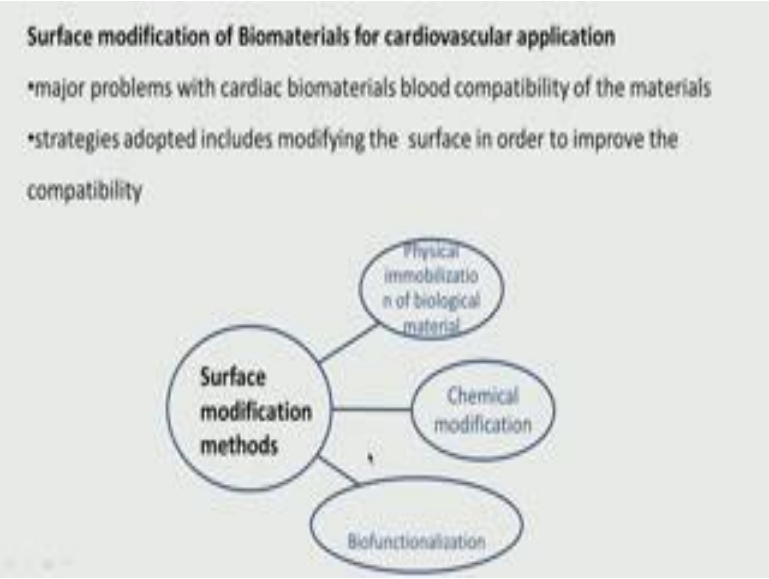

So, you need to do quite a lot of surface modification because the material has to be in contact with the blood. So, you have to make it blood compatibility whereas, in the other places we looked at bacterial biofilm issues and inflammatory issues and so on. So, we need to here look at blood compatibility, hemolysis and so on actually. So, different types of modification, we will spend a lot of time on surface modification could be physical, chemical or bio functional type of modification.

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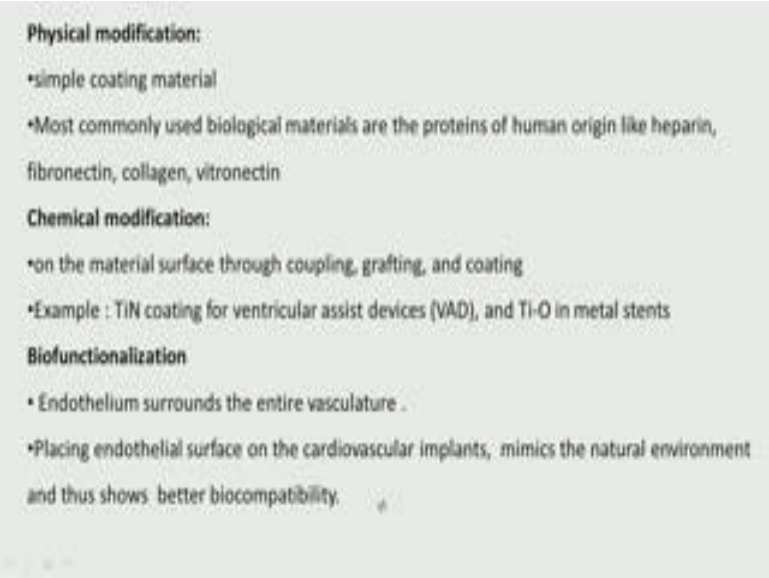

Physical could be simply quoting a material like quoting heparin. Heparin is used quite a lot as the anticoagulant, fibronectin, collagen, vitronectin and so on. Chemical means you couple material or you graft the material, that is the chemical modification like titanium nickel coating for ventricular assist devices and titanium oxide on metal stents, these all chemical. Biofunctionalization endothelium surrounds the entire vasculature, placing endothelial surface on the cardiovascular implants, mimics the natural environment and thus allows better bio compatibility.

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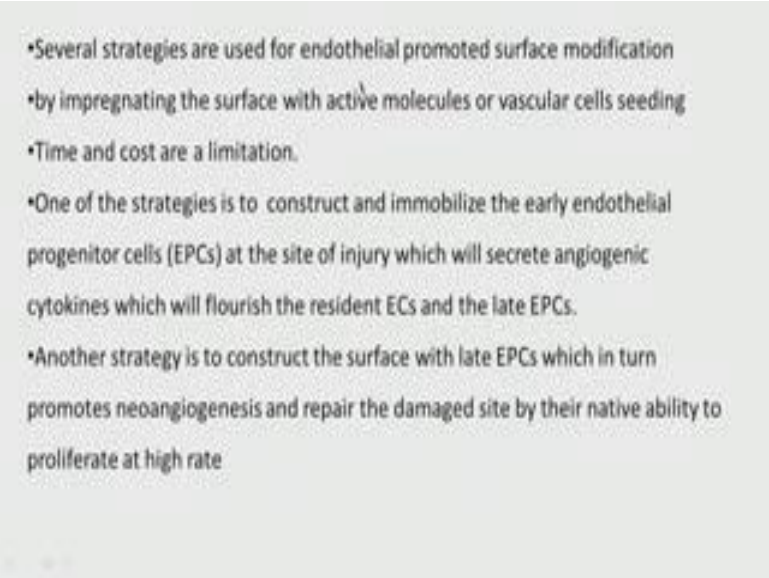

So, several strategies are used for endothelial promoted surface modification by impregnating the surface with active molecules or vascular cell seeding, but of course, it is very expensive and time consuming. So, we can construct and immobilize early endothelial progenitor cells at the site of injury, which will secrete angiogenic cytokines which will flourish the resident and the late EPCs, ECs and EPCs. Where, they are still under research and they have been tested quite a lot on animal models, but not on human volunteers. Another strategy is to construct the surface with the late EPCs, endothelial progenitor cells which in turn promotes new angiogenesis and repair the damaged side by their native ability to proliferate. So, we looked at different types of materials that are used in cardiovascular, that is surround the heart, the valves, the diaphragm, the shunts, the stents and then of course, biologically derived material, trying to grow cells on top of some scaffold, injectable biomaterials, taking care of infarcts, taking care of wounds and so on actually.

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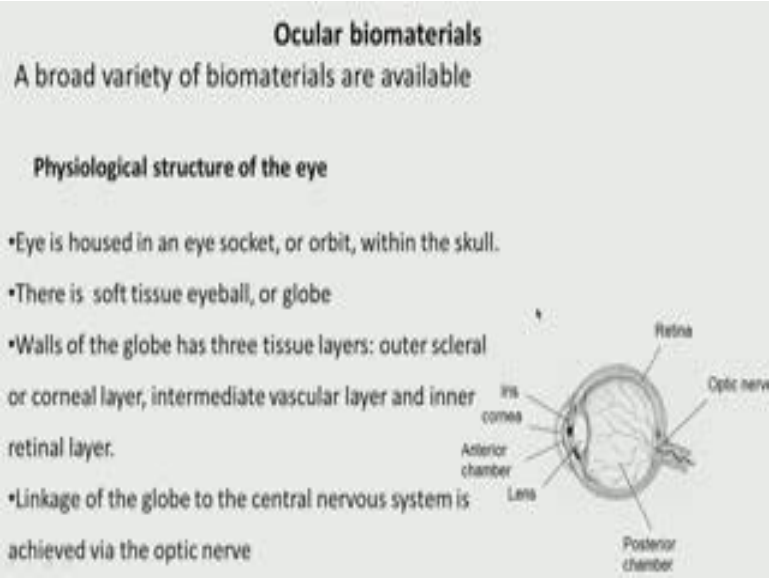

Next look at some biomaterials that are used in the ocular; that means, the eye. So, basically as you can see the retina is here, you have the optical nerve which connects to the brain. This is the posterior chamber, this is the anterior chamber, here the iris, the cornea here and the lens; this is the lens. So, there is lot of biomaterials used in this place in the eye. It is housed in a socket or orbit within the skull. So, we call this orbit within the skull and there is a soft tissue eye ball or a globe.

Walls of the globe has three layers; outer scleral or corneal layer, intermediate vascular layer and inner retinal layer. You can see the inner 1, 2, 3 here; linkage of the globe to the central nervous system is achieved via this optical nerve. So, there are lot of biomaterials trying to replace in this area.

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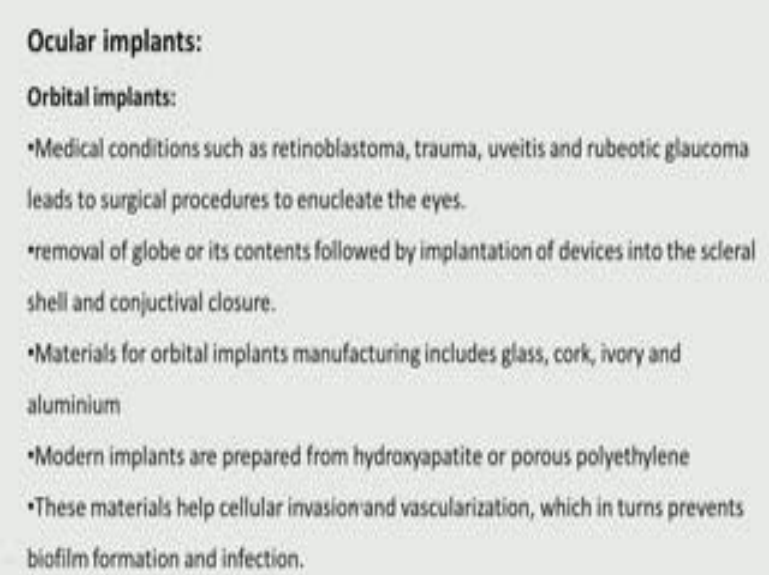

Ocular implants; orbital implants that is orbit this portion right. So, that is orbital implant. So, if there are retinoblastoma, trauma, uveitis, rubeotic glaucoma, then you need to remove whatever is inside and place orbital implants. So, we remove the globe or its contents followed by implantation of devices into this scleral shell and conjuctival closure. So, glass, cork, ivory, aluminum, then modern implants are hydroxyapatite or porous polyethylene. These materials help cellular invasion and vascularization which in turn prevents biofilm formation and infection. So, these biomaterials are not meant to help the patient to see, but they are used just to fill up the actual the orbit. So, originally some inorganic glass and ivory and aluminum are used later on hydroxyapatite or polyethylene were used. So, that there is a vascularization taking place also it will prevent the biofilm formation and infection.

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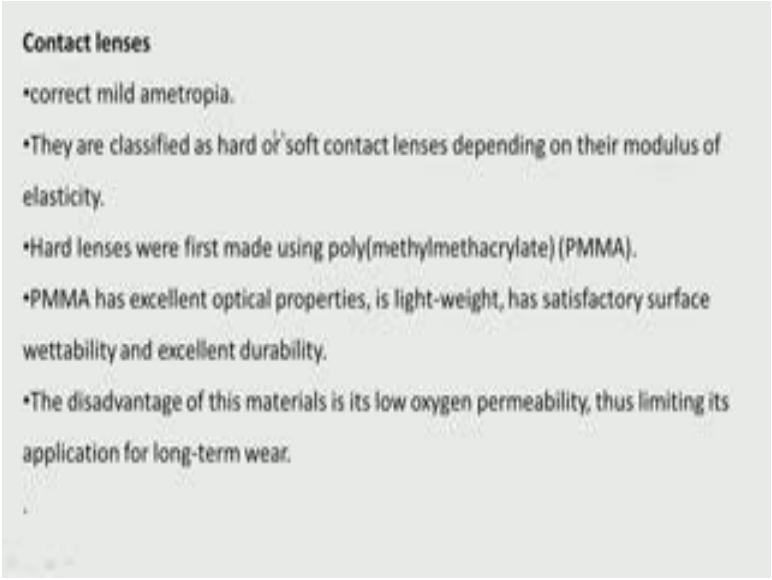

Contact lenses; this is mostly for correcting mild ametropia. So, you have hard, soft; hard lenses are using polymethylmethacrylate. They have very good excellent optical properties light weight, satisfactory surface, wettability. The main disadvantage is they have got very low oxygen permeability. So, the patient cannot bear it for a very long time, eyes become red.

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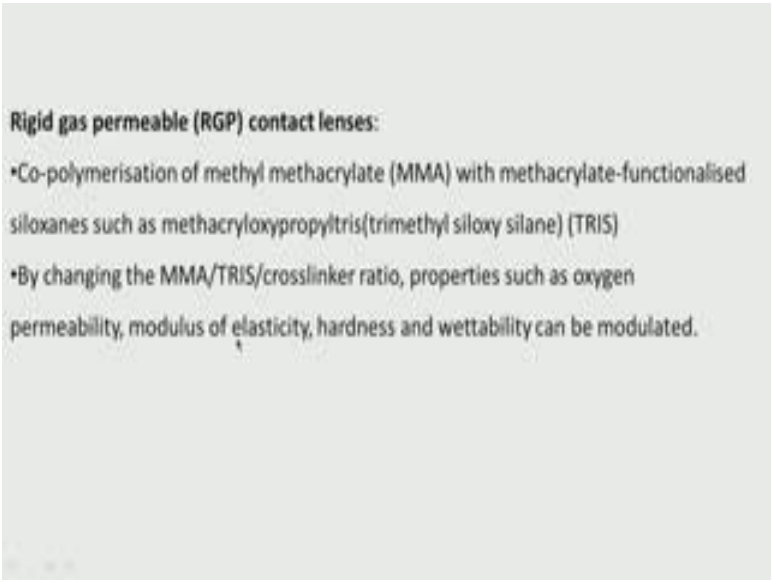

So, these rigid gas permeable contact lenses came in to picture. So, it is a co polymerization of methyl methacrylate with methacrylate functionalized siloxanes such

as methacryloxypropyltris; TRIS it is called. So, you copolymerized methyl methacrylate with the siloxanes, trimethyl syloxy silane.

So, when you do that. So, we can change the cross linker ratio. So, the oxygen permeability can be modified elasticity, modulus of elasticity can be modified, hardness wettability can be modified. That is called the rigid gas permeable contact lenses.

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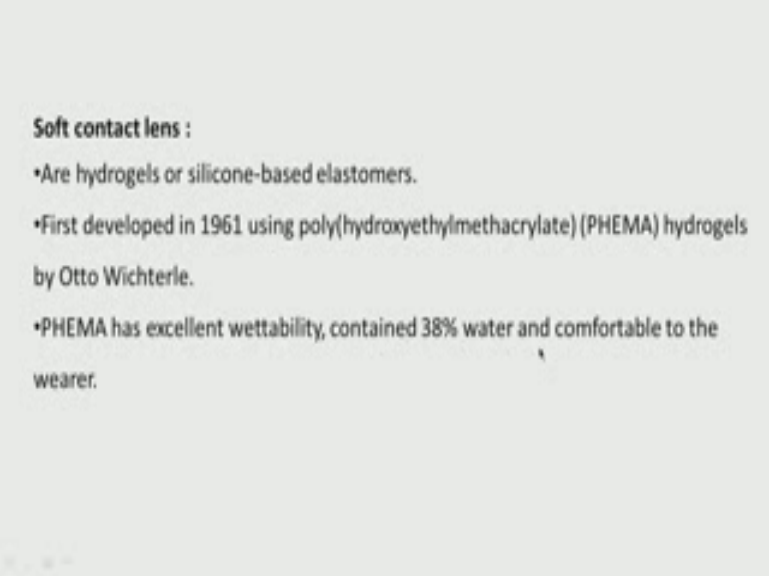

You also have these soft contact lenses. These are all hydrogels or silicone based material polyhydroxyethylmethacrylate, hydrogels discovered in 1961. They are very good wettability contains 38 percent water, comfortable to the wearer. So, that is the soft contact lenses.

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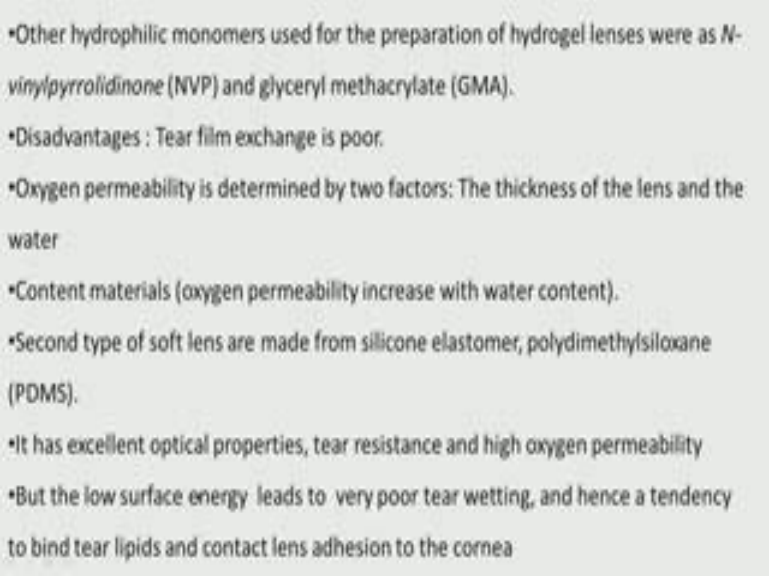

So, other hydrophilic monomers used for the preparation of hydrogel lenses are N vinylpyrrolidinone, glyceryl methacrylate. Of course, one disadvantage is the tear, they can get torn. The oxygen permeability which is very very important in contact lenses, it depends on the thickness of the lens and the amount of water that presents. So, oxygen permeability increase with water content, second type of soft contact lenses are made of silicone elastomer, polydimethylsiloxane; PDMS. The first type is polyhema, second type is polydimethylsiloxane. It has excellent optical properties and also good tear resistance and high oxygen permeability, but the low surface energy leads to very poor tear wetting and hence a tendency to bind tear lipids and contact lens adhesion to the cornea. So, the low surface energy means it has got very high contact angle. So, when teardrops come down, it does not wet properly.

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Commercially available lenses	Company	Material	Water content (%)	Oxygen Permeability (Dk)
Hard lenses				
Polycon II	PBH	TRIS-based silicone acrylate	0	12
Fluorocon	PBH	Fluorosilicone	0	60
Advent	3M Corp	Fluoro polymer	0	95
Quantum II	Bausch & Lomb	Silicone acrylate	0	100
Soft lenses				
Acuvue	Vistakon	HEMA/MAA	58	24
Seequence	Bausch & Lomb	HEMA	38	8.4
Actifresh 400	Hydron	MMA/NVP	73	36
Actosoft 60	Hydron	HEMA/GM	60	21
Silsoft	Bausch & Lomb	PDMS	0.2	340

So, the lipids get bound, they get adhere to the cornea. So, there are many companies which make this contact lenses as you can see from here list. I mean you do not have to bother much, but basically look at this silicone acrylate, fluoro silicone, fluoro polymers, silicone acrylate, HEMA, pyrrilidone, PDMS based materials; so lot of materials. So, and if you look at the water content mostly the soft contact lenses you have very high water content. Look at the oxygen permeability is fantastic, when you have PDMS water content is low, oxygen permeability is very high because it become very hydrophobic water content is very poor, but then oxygen permeability is very very high. So, if you want to have a balance here you know some of these methyl methacrylate, N vinylpyrrolidone, water content is also high, oxygen permeability is also high.

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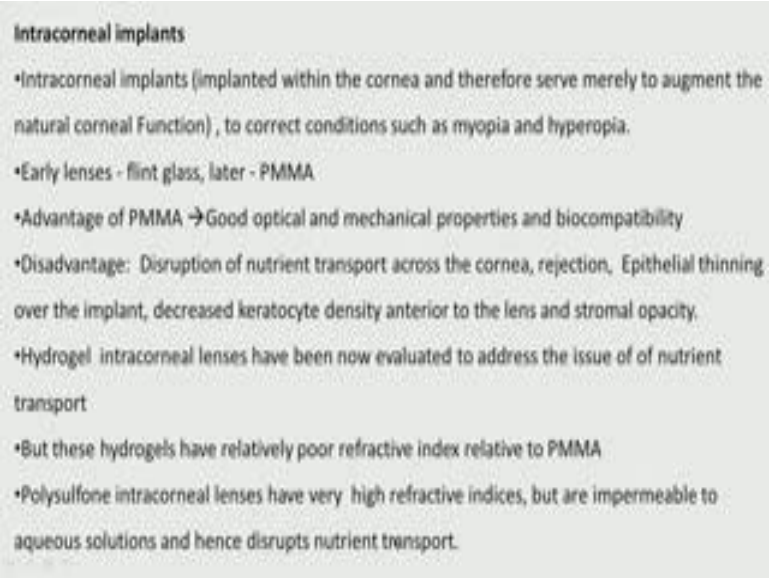

Intra corneal implants implanted within the cornea and therefore, so merely to augment the natural corneal function. T o correct conditions such as myopia and hyperopia made up of flint glass then PMMA. PMMA as I have been talking good optical mechanical properties, biocompatible. Disadvantage disruption of nutrient transport across the cornea, rejection, epithelial thinning over the implant, decreased kerotocyte density anterior to the lens and stromal opacity. So, hydrogel intra corneal lenses now are being looked at to improve the nutrient transport, but then of course, these have very poor refractive index when compared to PMMA type.

Polysulfone intracorneal lenses have very high refractive indices, but are impermeable to aqueous solution and hence prevents nutrient transport. So, there is some problem if you are looking at hydrogels or if you are looking at PMMA or if you are looking at polysulfone based material. PMMA has very good optical properties, but the problem of nutrient transport hydrogels they have very poor refractive index, but nutrient transport is very good.

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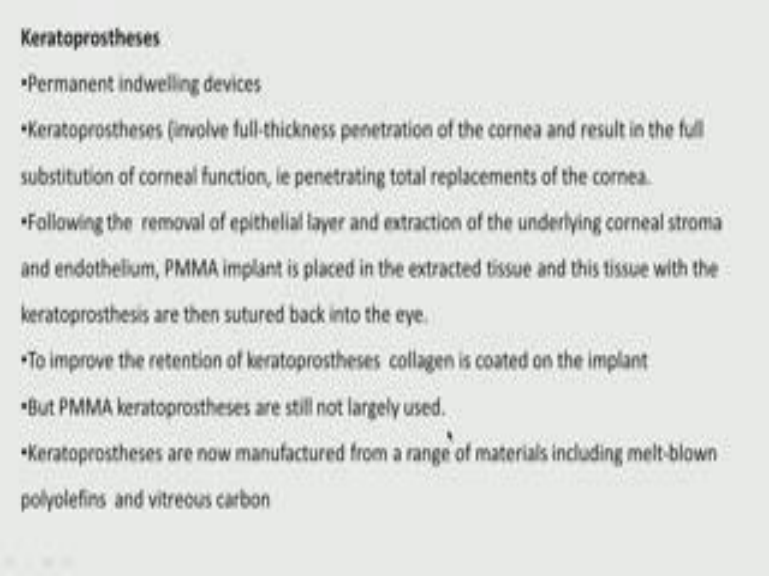

And keratoprosthesis, what is this? This is a permanent indwelling device; this involves full thickness penetration of the cornea and result in the full substitution of the corneal function. That is penetrating total replacements of the cornea, following the removal of epithelial layer and extraction of the underlying corneal stroma and endothelium PMMA implant is placed in the extracted tissue and this tissue with the keratoprosthesis are then sutured back in to the eye. That is called keratoprosthesis. These carried out to improve the retention of keratoprosthesis collagen is coated on the implant, but PMMA keratoprosthesis are still not largely used. These are now made from quite a lot of material like polyolefins and vitreous carbon and so on actually.

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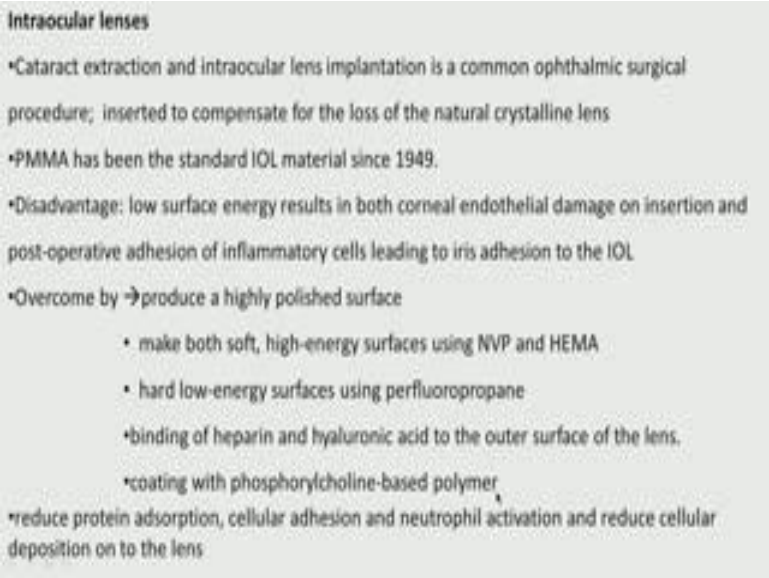

Intraocular lenses that is cataract extraction after that they place a lens, intraocular lens. It is called is a very common nowadays, it is an ophthalmic surgical procedure. This is inserted to compensate with the loss of the natural crystalline lens.

PMMA has been the standard for a very very long time. Low surface energy results in both corneal endothelial damage or an insertion and postoperative adhesion of inflammatory cells leading to iris adhesion to the IOL; that is intraocular. So, how do they overcome? They produce high polished surface, make both soft high energy surfaces using N vinylpyrrolidone and HEMA, hard low energy surface using perfluoropropane, binding of heparin and hyaluronic acid to the outer surface of the lens, coating with phosphorylcholine based polymers. So, different types of approaches are being used actually.

So, reduce protein adsorption, cellular adhesion and neutrophil activation, reduce cellular deposition on to the lens. So, we looked at some of the biomaterials used in ocular region as you can see PMMA is used because of its very good optical properties, but then it has got some disadvantages, especially in oxygen transport and so on and then we have soft contact lenses which will retain what are quite a lot like your HEMA. Then we also talked about nutrition, diffusion becomes a problem. So, you need to balance between all these various factors to achieve a good device to be placed in the eye region.

Thank you very much for your time.