Artificial blood vessels

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1. Improvement of existing synthetic grafts:

Surface coating with bioactive molecules improve the properties of vascular grafts. Growth factor like fibroblast growth factor and proteins like albumin, gelatin, collagen, heparin, recombinant-hirudin and peptide like YIGSR and RGD, antibiotics like vancomysin, rifampin and cephalosporin improved the endothelialisation of the synthetic grafts thereby reducing the thrombosis. Due to the less significance of these synthetic grafts for < 6mm, alternative source of material should be explored for their utility in preparing tissue engineered vascular grafts (TEVG). The wide range of polymeric materials employed in the vascular graft preparation is tabulated.

The biodegradable polyesters like poly lactic acid and poly glycolic acid or in their combination with other polymer systems like polycaprolactone improves the durability of the grafts by providing the properties of more than one polymer. The mechanical strength of the synthetic polymer is always higher than the natural polymers due to presence of rigid chemical backbone. These polymers can be tailored to expect the degradation rate matching to the host tissue. The fabrication technique employed to process these polymers will further improve the properties such as mechanical, topography (alignment and fibrous), and also porous characteristics. The polymers employed in the development of synthetic grafts can also be used to deliver drughs such as anti-thromobogenic agents at the site of damage and promotes the repair effectively. For example the nitric oxide releasing vascular grafts prevent effectively the thrombogenic factors attachment on the grafts and release of specific endothelial growth factor helps in the recruitment of endothelial cells from circulation blood. The cellular infiltration in these polymeric scaffolds promotes the dense packing of the cells in three-dimensions which helps in secreting their own extracellular matrix, which promotes the regeneration of repair tissue.

Biodegradable polymer	Natural polymer
Poly glycolic acid	Collagen
Poly lactic acid	Elastin
Poly caprolactone	Fibrinogen
Poly lactic-co-glycolic acid	Silk fibroin
polydioxane	Chitosan
Poly hydroxyalkonate	Glycosaminoglycans
Segmented polyurethanes (nitric oxide relasing)	Hyaluronate

Table 1: List of polymeric and natural material used for the preparation of vascular graft

2. Characterization of the Tissue engineered vascular grafts

To be functional *in vivo* the tissue engineered vascular grafts has to undergo complete testing to check its mechanical, physical and chemical properties.

2.1 Mechanical strength:

a. Developing the successful graft with adequate mechanical strength to withstand the pressure developed during the constant blood flow is really tough to achieve. Though the developing scaffold possess adequate i.e lesser porosity, which can brings down the mechanical strength. Hence mechanical properties such as ultimate tensile strength, elastic modulus, compliance testing, suture retention strength, dynamic fatigue test and also burst pressure should be thoroughly evaluated as follows.

(i) Ultimate tensile stress:

The native arterial blood vessels have an ultimate tensile strength of 2.24 MPa and the decellularized tissue have 4.34 MPa. It is essential for the

artificially prepared vascular graft to maintain a load bearing capacity in this range.

(ii) Young's Modulus:

The modulus from the stress-strain curve can be split into two based on the extracellular composition. The native tissue has an initial modulus 0.71 MPa is due to the elastin network whereas the 12.26 MPa is due to the collagen network. The modulus value for decellularized tissue is found to be 1.11MPa and 19.81MPa for elastin and collagen respectively. Hence the elasticity of the tissue is purely based on the ratio of various extracellular matrix proteins present.

(iii) Compliance testing:

As per the American National Standard Institute (ANSI) 7198, the vascular graft should be subjected to tension with a load of 0.460N and phosphate buffered saline should be made to flow within the graft at a pressure of 50-200 mmHg. Then the external diameter of the graft at two extreme time points will be measured with the following formulae:

$$\% \text{ compliance/100 mmHg} = \frac{(R_{ip2} - R_{ip1})/R_{ip1}}{p2-p1} \times 10^4$$

Where *p1*= lower pressure, *p2*= higher pressure, R_{ipx}= internal radius at pressure x and calculated by the formula

$$R_{ipx} = \sqrt{R^2_{0px} - (R_i + t_0)^2 + R^2_i}$$

Where R_{0px} = measured external radius at pressure x, R_i= measured internal radius at rest, t_o= measured wall thickness at rest

The compliance in native blood vessel is in connection with the extracellular matrix elastin and the vascular medium.

(iv) Suture retention testing:

This test will be essential to evaluate the material for resisting the tension during implantation. One end of the vascular graft will be fixed to the static grip of uniaxial mechanical tester, whereas the other end of the graft will be pierced by a suture needle and pulled along with the dynamic grip of the

tester at a constant speed. Thereby the suture retention strength can be calculated from the obtained stress-strain curve.

(v) Dynamic fatigue testing:

In order to mimic the blood vessel mechanics, cyclic loading to the vascular grafts should be performed in pressurized reservoir. The pressure difference between two walls of the graft will be recorded using pressure transducer. The cyclic pressure can be varied from 120/80mmHg at 1 Hz for stipulated days.

(vi) Burst pressure analysis:

In order to find out the leaky site in the vascular graft the burst pressure analysis has to be performed by the flow of simulated fluid at a controlled pressure of 80-100 mm Hg/s. The maximum pressure at which the graft to burst will be recorded as the burst pressure except at the site of cannulation. Keeping the constant wall thickness in all the grafts the burst pressure should be calculated as

Burst pressure = material yield stress x thickness/ radius

The native veins with a diameter of 2-3mm is calculated to have a burst pressure of <1600 mmHg.

2.2 Porosity and pore diameter:

The success of vascular tissue engineering is also determined by the pore size and porosity of the scaffolds. Generally, porous nature of scaffold is essential for tissue engineering applications since it contributes the vascularisation; cell infiltration along with the nutrient diffusion. However, in case of blood vessel regeneration, the porous nature of scaffolds may also contribute the leaky vessels. Hence care must be take to design a scaffold with optimal porous characteristics for the successful graft development. This can be evaluated by mercury extrusion porosimeter by following means. Very small pore size ranging from 0.003 to 1000 µm can be detected by this method, which is based on the principle of applying nitrogen pressures at various levels ranging from 0.2psi to 50psi to the mercury filled samples. Intrusion of mercury into the sample pores at controlled pressure gives the pore size, pore volume and porosity of the sample.

2.3 Current research

In order to exactly mimic the native blood vessel architecture, advanced fabrication technology has to be employed. The nanofibers fabricated by electrospinning provide a unique three dimensional topographic cues with no compromise in the mechanical strength and porosity. The functional endothelial and smooth muscle cells were successfully grown which exhibited the alignment equivalent to the native blood vessel. Thus the tubular grafts have a very high potential to be used as tissue engineered vascular graft.

The following properties very essential to generate a successful vascular graft

- Less thrombogenic/ biocompatible
- Endothelial cell recruitment
- Controlled release of factors from grafts for repair and regeneration
- Biodegradable
- Easy to handle
- Mechanical properties matching to blood vessels

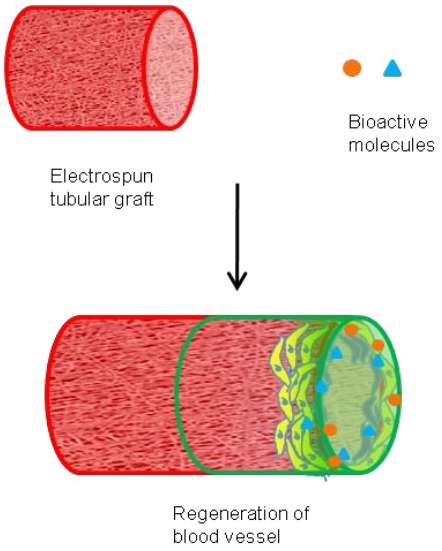

Fig 3: Tissue engineering strategies to regenerate the blood vessel

Future research strategies involve the loading vasoactive factors loaded in hydrogel scaffold made of natural collagen and proteoglycan derivatives. These scaffolds could mimic the elastic nature of native blood vessel and loaded factors prevent thrombosis and aid the endothelialisation.