Blood Vessel Nomenclature for Tissue Engineering

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Abstract:
There is a strong demand for vascular grafts due to arteriosclerosis and other cardiovascular diseases (CVD) that are the main cause of mortality. Auto transplantation of blood vessels which is usually performed have its own limitations because of short availability of autologous blood vessels. This led to use of non biodegradable synthetic prostheses and, more recently, to the approach of tissue engineering. In tissue engineering of blood vessels (TEBV) three components are used (a) cells, (b) scaffolds or matrices (c) environmental factors such as compression, she a stresses. In this review we present with anatomical and functional details of blood vessel principles of TEBV ,biological requirements of TEBV and thus nomenclature of TEBV depending upon the type of cell used, preclinical and clinical studies in TEBV, present status ,imitations and future prospects of TEBV.

I. INTRODUCTION
One of the foremost cause of deaths in patients over the age of 65 years is CVD. Regardless of advancements in the medical treatment of CVD, the number of vascular intervention and reconstruction like bypass grafting and angioplasty with or without stent has increased in past years. These measures are to be undertaken particularly in those patients who are less likely to have enough vein for use as a conduit for revascularization. These days autologous arteries or veins are the widely used for coronary and peripheral bypass procedures. There are limitations to autologous vessels. In some patients, it is not available due to vessel disease, previous surgery or trauma. The replacement of large diameter vessels (>6 mm) like aorta can be performed using polymer prosthetics with long-term patency. There is evidence that synthetic polymer grafts have rapid thrombus formation and intimal hyperplasia subsequent to bypass surgery, limiting their utility in some cardiac and cerebral vessels less than 6mm diameter or in areas of low blood flow. Other limitations of synthetic vascular grafts are risk of bacterial infection and inflammatory hyperplasia of intima of vessel. These drawbacks, led to development of a new approach for tissue regeneration, tissue-engineered blood vessel (TEBV).In this approach the blood vessel is vasoactive, matches the biomechanical aspects of healthy artery and is capable of growth, remodeling. In vitro construction of blood vessels with collagen and cultured bovine aortic endothelial cells (ECs), smooth muscle cells (SMCs) and adventitial fibroblasts was first reported by Weinberg and Bell in 1986. Globally there has been considerable progress in the area of vascular engineering over the past two decades. To date, the TEBVs could be successfully constructed in vitro, and be used to repair the vascular defects in animal models. However, only a few have achieved clinical success with this approach. This review aims to describe the major progress in the field of tissue engineering in blood vessels with coverage of anatomy of blood vessels, the principles along with engineering requirements for implantation of tissue-engineered grafts like seeding cell sources, the biodegradable scaffolds, the construction technologies, clinical application the shortfalls of autologous and synthetic grafts and current status of tissue-engineered blood vessel research.

Anatomical and functional details of human blood vessel
The large medium and small arteries are made of three layers, called from the luminal side outward, the tunica intima, the tunica media and the tunica adventitia. The veins; capillaries, don't have three layers. The vascular wall except that for capillaries is composed of three types of cells: the endothelial cells (ECs) that lined in the tunica intima, the smooth muscle cells (SMCs) that predominantly located in the tunica media and the adventitial fibroblasts in the tunica adventitia. Among them, ECs and SMCs play a key role in keeping the integrity of the vessel and maintaining its mechanical properties. The endothelium layer provides a continuous selective permeable, thrombo-resistant barrier that facilitates laminar blood flow through the blood vessel. It also controls vessel tone, platelet activation, adhesion and aggregation, leukocyte adhesion and SMC migration and proliferation. SMCs have secretory capabilities. The collagen fibres, elastin fibres, elastic lamellae and proteoglycans secreted by the SMCs keep the elasticity and radial compliance of the vessel.

Principle of TEBVs
The first step is to seed cells on biodegradable scaffolds followed by in vitro culture or in vivo implantation. The scaffolds are reabsorbed, leaving only the new tissue generated by the cells. (Fig 1).

The positive results of tissue regeneration relies on the proper seeding of cells, the scaffolds and the construction technologies. Functional TEBVs should be non-thrombogenic, non-immunogenic, compatible at high blood flow rates and have similar viscoelasticity to native vessels. Furthermore, the grafts should be living tissues that could eventually integrate into the body and become indistinguishable from the native vessels. It has been accepted that the functional TEBVs cannot be achieved without ECs, SMCs, biodegradable scaffolds and the unique vessel-engineering techniques.
Biological requirements and nomenclature of TEBV

Seeding cells sources
- Autologous ECs and SMCs
- Embryonic stem cells
- Adult stem cells
- Other cell types

Seeding cell sources
Ideally it should be non-immunogenic, functional expand in culture. Mature vascular cells, embryonic and adult stem cells, as well as alternative cell types that could possibly replace the ECs and SMCs, have been tried in vessel engineering.

Autologous Endothelial Cells(ECs) and Smooth Muscle Cells(SMCs)TEBV
Non-immunogenic ECs and SMCs isolated from auto log ousvessels have been well used for engineering new vessels in many studies. [8, 14–17]. The limitations found in these studies were inability to obtain large amount of cells from a small vessel biopsy. Even the cells isolated from umbilical veins have limited proliferation potential. In addition, cells would lose their function during in vitro expansion. Mckee et al. and Shao et el did genetic manipulation by introducing human telomerase reverse transcriptase subunit (hTERT) into human SMCs. They reported that cells could proliferate far beyond their normal lifespan and retained their characteristics of normal control cells [18,19]. Long term follow up studies are necessary before clinical application. Allergenic ECs and SMCs is another source for vessel engineering. However, immuno-rejection problem could not be avoided in this case, especially for ECs that contact directly with blood cells. To date, there is no promising way to solve the cell proliferation problem. It is of great interest to find alternative cell sources for vessel engineering.

Stem cells (Embryonic & Adult) TEBV
Recently embryonic and adult stem cell has become a major cell source for TEBV[20–22]. Embryonic stem (ES) cells are able to produce all types of cells, while adult stem cells are normally limited to certain lineages. The advantage is that these cells are able to self renew and differentiate into mature cells in the proper conditions, which makes it possible to obtain large amount of functional cells for tissue regeneration. Differentiation of ES cells into ECs and SMCs has been studied widely in mouse models. The foetal liver kinase-1(Flk-1) positive cells from differentiated ES cells, containing EC and SMC progenitors, could participate the neovascular formation when injected into animal bodies [23–28]. High purity of functional ECs could be achieved from differentiated mouse ES cells without genetic manipulation by McCloskey et al.[29]. Levenberg et al. showed that human ES cells could be differentiated into ECs that are able to form tube-like structures on matrigel, and form micro vessels when used in mice models[30]. ESs is good seeding cell source for vessel engineering with the drawback of ethical issue because we need to destroy human embryo which is in some religion considered destroying a life. It is still far away from clinical application. The other hurdles are immunogenic and tumourgenic problems. Comparing with ES cells, adult stem cells can be obtained from patients themselves, avoiding the immuno-rejection, tumorgenic capacity and ethical problems.
Figure 2. Stem cell as source of TEBV

**Endothelial progenitors cells (EPCs) TEBV**
EPCs exhibited contractile activity and nitric oxide mediated vascular relaxation that were similar to native carotid arteries and are therefore a good EC source for vessel engineering. EPCs from bone marrow or umbilical cord blood are type of the adult stem cells that have the capacity to proliferate, migrate and differentiate into mature ECs. Granulocyte macrophage colony stimulating factor (GM-CSF) or Vascular endothelial growth factor (VEGF) are used for mobilization of EPCs into peripheral blood[31-35]. EPCs of blood of sheep have been used to construct an engineered vascular graft in vitro.[36]

**Bone marrow derived mesenchymal stem cells (BMSCs) TEBV:** ECs and SMCs derived from bone marrow of dogs have been successfully engineered as small-diameter vascular grafts in vitro and in vivo[37-41].

**Adipose tissue derived tissue engineered TEBV**
Microvascular ECs could be developed from human adipose tissue by CD34 expression [42-44]. Zuk et al. isolated another multi-potent population termed 'adipose derived stromal cells (ADSCs)' from adipose tissue, which can differentiate into adiposity, osteoblasts and muscle cells [45]. Wen Jie Zhang et al have mentioned about their unpublished data on ADSCs where they successfully constructed elastic vessel wall in a bioreactor by seeding those cells on polyglycolicacid (PGA) scaffold [46]. Long term fate of both BMSCs and ADSCs is unclear hence there is need of follow up studies in animal models.

**Adult human fibroblasts derived TEBV**
Some scientists tried to derive TEBV from adult human fibroblasts and my fibroblasts extracted from skin biopsies, which were used as arterial bypass grafts in long-term animal models [47, 48]. These TEBVs were anti-thrombogenic and mechanically stable with good patency rates. No human studies are reported.

**Biodegradable scaffolds**
Biodegradable scaffold is a biocompatible 3-dimentional template in TEBV which supports cell growth, migration, differentiation and secretion of extracellular matrix (ECM) directing new tissue formation. The scaffolds are slowly resorbed in culture or after implantation, leaving only the tissue generated by the cells. The scaffolds made up of collagen, elastin, fibronectin were used by Weinberg and Bell [18]. The scaffolds made up of dacron mesh or polyurethane, fibrin gels decellularized tissue were tried later.
Current status utility of TEBV in patients
To date, TEBVs could be successfully constructed in vitro and in animal models, with few clinical studies reported as successful for clinical applications of engineered vessel grafts without exogenous scaffolds and achieved vessel regeneration without in vitro culture.

Prospects of TEBV in CVD
Over the past years interest in blood vessel tissue engineering has risen on a worldwide level with successful results in preclinical studies and very few clinical implants. The prerequisite of TEBV is it should have good mechanical strength, non-thrombogenic, and vasoreactive. With modification in technologies of material science to create a scaffold by delicate design and modified method to promote the SMCs and EC migration for preventing thrombosis at the time of implantation the day is not far we could reach heights in this particular field.

II. REFERENCES
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