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Cardiovascular Tissue Engineering: Where We Come From and Where Are We Now?

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Tissue engineering was introduced by Vacanti and Langer in the 80's, exploring the potential of this new technology starting with the well-known "human ear on the mouse back". The goal is to create a substitute which supplies an individual therapy for patients with regeneration, remodeling and growth potential. The growth potential of these subjects is of special interest in congenital cardiac surgery, avoiding repeated interventions and surgery. Initial applications of tissue engineered created substitutes were relatively simple cardiovascular grafts seeded initially by end-differentiated autologous endothelial cells. Important data were collected from these initial clinical autologous endothelial cell seeded grafts in peripheral and coronary vessel disease. After these initial successfully implantation bone marrow cell were used to seed patches and pulmonary conduits were implanted in patients. Driven by the positive results of tissue engineered material implanted under low pressure circumstances, first tissue engineered patches were implanted in the systemic circulation followed by the implantation of tissue engineered aortic heart valves. Tissue engineering is an extreme dynamic technology with continuously modifications and improvements to optimize clinical products. New technologies are unified and so this has also be done with tissue engineering and new application features, so called transcatheter valve intervention. First studies are initiated to apply tissue engineered heart valves with this new transcatheter delivery system less invasive. Simultaneously studies have been started on tissue engineering of so-called whole organs since organ transplantation is restricted due to donor shortage and tissue engineering could overcome this problem. Initial studies of whole heart engineering in the rat model are promising and larger size models are initiated.

MeSH Keywords: Cardiovascular Diseases • Cardiovascular Surgical Procedures • Endothelial Cells • Tissue Engineering

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Tissue engineering was introduced in the mid 80's by Vacanti and Langer, exploring the potential of this new technology and starting with the famous "human ear on the mouse back" [1]. After this initial study, Vacanti's group [2] started investigate the potential advantages of tissue engineered modified heart valves. During the same period, Nerem et al. [3] initiated at the same time cell engineering to create blood vessel substitutes. The goal of this promising technology, called tissue engineering, is to create unique substitutes allowing individual patients therapy with regeneration, remodeling and growth potential. Practically, patient's healthy cells and/or tissue will be harvested, *in vitro* cultured and multiplied, and at the time a sufficient number of cells is available, a 3-dimensional scaffolds can be seeded, to restore the functionality of deteriorated tissue. Growth potential of these subjects is of special interest in congenital cardiac surgery, avoiding repeated interventions and/or surgeries.

Initial clinical application of tissue engineered created substitutes were relatively simple and therefore did not completely fulfill the criteria of be a tissue engineered device, but were an initial step to implement a new era into medical therapy. These *in vitro* seeded grafts were used to bypass below-knee vascular disease as surgical outcome is generally unsatisfying, especially in small diameter grafts, and final lower leg amputation is needed [4–6]. Initial studies of Zilla [7] showed the impact of endothelial cells, better endothelium, on the optimal functional of the cardiovascular system and therefore the impact during bypass grafting in which generally graft materials are used within endothelial cells. Therefore Deutsch et al. [8] started to implement autologous endothelial cell seeding on graft conduits prior to below-knee bypass grafting. This important studies showed not only the significant improvement on the patency rates of these endothelial cell seeded grafts, compared with unseeded grafts, but also the complexity of these *in vitro* constructed viable graft conduits. Data resulting from these study were of great importance for further development of tissue engineering cardiovascular produces. Furthermore this study showed that endothelial cells behave different *in vitro* as *in vivo*. One reason was due to contamination of fibroblast who easily overgrow endothelial cells. Additionally high lipid levels in autologous serum decrease or stops endothelial cell growth *in vitro* [9]. During cardiac surgery, especially in redo-operation there is not always sufficient graft material available and since the SYNTAX study showed in specific patient population better long-term outcome of coronary bypass surgery compared with coronary artery stenting [10], additional graft material were needed. Konertz et al. [11,12] started *in vitro* seeding of 4-mm e-polytetrafluoroethylene grafts which were *in vitro* seeded with autologous vascular endothelial cells. Later on also xenogenic grafts were used as a scaffold since a better hemostasis can be achieved [13]. The patency rates of these endothelial cell seeded grafts were remarkable, however the disadvantage was the time delay until implantation. Therefore new cell sources are needed without losing cell functionality. Today however due to hybrid treatment in coronary artery disease improvement, there is limited need for these demanding grafts [14]. Most important would be that these seeded grafts would be intra-operative available. This would be of more interest for surgery of peripheral vessels allowing improved long-term graft patency.

During this development on these vascular grafts, Vacanti et al. [15] started creating tissue engineering of heart valves and implanted valvular leaflets into a lamb model. The scaffold used for these heart valves were created of biodegradable polymers which were *in vitro* seeded with autologous endothelial and interstitial valvular cells. Shinoka [16] presented first results of these tissue engineered heart valves which were implanted into the right ventricular outflow tract of the juvenile sheep model. Afterwards first clinical implants were successfully performed using *in vitro* seeded bone marrow cells onto synthetic patches or pulmonary artery [17,18]. Our group [19] implanted successfully an autologous vascular endothelial cell seeded pulmonary decellularized cryopreserved allograft during the same period of time, showing excellent behavior of these tissue engineered heart valve after 10 years of follow-up [20]. Cebotari et al. [21] published in 2006 the clinical implant of autologous progenitor cell seeded decellularized allograft.

After obtaining successfully results in experiment model and small clinical trials, first tissue engineered cardiovascular constructs were implanted into the systemic circulation of experimental models. Tissue engineered patch materials sutured into the descending aorta [22], showing absence of aneurysm formation or early deterioration and complete recellularization after short period of implantation. Afterwards tissue engineered heart valves were implanted into the aortic position performing a subcoronary implantation technique [23], but also as root replacement [24] allowing the valve wall systemic pressurized. Zehr et al. [25] implanted first unseeded decellularized aortic allografts in patients, with excellent results. These studies were all performed with tissue engineered heart valves based on decellularized scaffolds [26]. Additional studies were know performed to study tissue behavior in the mitral position of experimental model, allowing highest tissue stress which can be addressed to tissue engineered heart valves [27]. It would be desirable to implant these heart valves minimally invasive without distortion of the tissue during the application.

Finally there is the era of whole organ engineering, in which the bio-artificial heart [28] is one important that could overcome the problem of organ shortage. Ott et al. [29] started with in the rat model, however larger organ sizes will be needed as other groups work on [30] which could be used for human recipients.

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References:

1. Vacanti CA, Langer R, Schloo B, Vacanti JP: Synthetic polymers seeded with chondrocytes provide a template for new cartilage formation. Plast Reconstr Surg, 1991; 88: 753–59
2. Shinoka T, Breuer CK, Tanel RE et al: Tissue engineering heart valves: valve leaflet replacement study in a lamb model. Ann Thorac Surg, 1995; 60: S513–16
3. Nerem RM: Cellular engineering. Ann Biomed Eng, 1991; 19: 529–45
4. Deutsch M, Meinhart J, Vesely M et al: *In vitro* endothelialization of expanded polytetrafluoroethylene grafts: a clinical case report after 41 months of implantation. J Vasc Surg, 1997; 25: 757–63
5. Zilla P, Fasol R, Deutsch M et al: Endothelial cell seeding of polytetrafluoroethylene vascular grafts in humans: a preliminary report. J Vasc Surg, 1987; 6: 535–41
6. Bradbury AW, Adam DJ, Bell J et al: BASIL trial Participants. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Analysis of amputation free and overall survival by treatment received. J Vasc Surg, 2010; 51: 18S–31S
7. Zilla P, von Oppell U, Deutsch M: The endothelium: a key to the future. J Card Surg, 1993; 8: 32–60
8. Deutsch M, Meinhart J, Fischlein T et al: Clinical autologous *in vitro* endothelialization of infrainguinal ePTFE grafts in 100 patients: a 9-year experience. Surgery, 1999; 126: 847–55
9. Meinhart J, Halbmayer WM, Deutsch M, Zilla P: Hyperlipidemia coincides with reversible growth impairment of cultured human autologous endothelial cells. Endothelium, 2002; 9: 239–46
10. Serruys PW, Morice MC, Kappetein AP et al, SYNTAX Investigators: Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med, 2009; 360: 961–72
11. Dohmen PM, Pruss A, Koch C et al: Six years of clinical follow-up with endothelial cell-seeded small-diameter vascular grafts during coronary bypass surgery. J Tissue Eng, 2013; 4: 2041731413504777
12. Dohmen PM, da Costa F, Yoschi S et al: Can autologous vascular endothelial cell seeding increase the patency rate of small-diameter No-React-treated bovine internal mammary arteries? An *in vivo* study in juvenile sheep. Med Sci Monit, 2007; 13(9): BR188–93
13. Dohmen PM, Gabbieri D, Lembcke A, Konertz W: Endothelial cell-seeded bovine internal mammary artery for complete revascularization. Ann Thorac Surg, 2007; 83: 1168–69
14. Gosev I, Leacche M: Revascularization: the future of coronary artery bypass surgery or an unfulfilled promise? Circulation, 2014; 130: 869–71
15. Langer R, Vacanti JP: Tissue engineering. Science, 1993; 260: 920–26
16. Shinoka T, Breuer CK, Tanel RE et al: Tissue engineering heart valves: valve leaflet replacement study in a lamb model. Ann Thorac Surg, 1995; 60: S513–16
17. Shin'oka T, Imai Y, Ikada Y: Transplantation of a tissue-engineered pulmonary artery. N Engl J Med, 2001; 344: 532–33
18. Shin'oka T, Matsumura G, Hibino N et al: Midterm clinical result of tissue-engineered vascular autografts seeded with autologous bone marrow cells. J Thorac Cardiovasc Surg, 2005; 129: 1330–38
19. Dohmen PM, Lembcke A, Hotz H et al: Ross operation with a tissue-engineered heart valve. Ann Thorac Surg, 2002; 74: 1438–42
20. Dohmen PM, Lembcke A, Holinski S et al: Ten years of clinical results with a tissue-engineered pulmonary valve. Ann Thorac Surg, 2011; 92: 1308–14
21. Cebotari S, Lichtenberg A, Tudorache I et al: Clinical application of tissue engineered human heart valves using autologous progenitor cells. Circulation, 2006; 114: I132–37
22. Dohmen PM, da Costa F, Lopes SV et al: Successful implantation of a decellularized equine pericardial patch into the systemic circulation. Med Sci Monit Basic Res, 2014; 20: 1–8
23. Dohmen PM, da Costa F, Yoshi S et al: Decelluarized xenografts implanted into the aortic position. J Clinic Experiment Cardiol, 2012, S: 004
24. Cebotari S, Tudorache I, Ciubotaru A et al: Use of fresh decellularized allografts for pulmonary valve replacement may reduce the reoperation rate in children and young adults: early report. Circulation, 2011; 124: S115–23
25. Zehr KJ, Yagubyan M, Connolly HM et al: Aortic root replacement with a novel decellularized cryopreserved aortic homograft: Postoperative immunoreactivity and early results. J Thorac Cardiovasc Surg, 2005; 130: 1010–15
26. Baraki H, Tudorache I, Braun M et al: Orthotopic replacement of the aortic valve with decellularized allograft in a sheep model. Biomaterials, 2009; 30: 6240–46
27. Honge JL, Funder JA, Jensen H et al: Recellularization of decellularized mitral heart valves in juvenile pigs. J Heart Valve Dis, 2010; 19: 584–92
28. Smit FE, Dohmen PM: Bio-artificial heart as ultimate treatment of end-stage heart failure. Med Sci Monit Basic Res, 2014; 20: 161–63
29. Ott HA, Matthiesen TS, Goh SK et al: Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart. Nat Med, 2008; 14: 213–21
30. Weymann A, Patil NP, Sabashnikov A et al: Bioartificial heart: A human-sized porcine model – The way ahead. PLoS One, 2014; 9: e111591

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