Small-Diameter Tissue-Engineered Vascular Grafts

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In general, arterial bypass grafting in the heart or below the knee requires small-diameter grafts. Thus, shortage of material for such surgeries remains a big challenge because autologous grafts are often not available in certain patient groups such as claudicants, patients with diabetics or vein disease, and in patients requiring reoperations. This has further underscored the need for developing alternative small-diameter vascular grafts. One candidate, small-diameter tissue-engineered vascular grafts (SD-TEVGs), is fabricated using novel techniques and interdisciplinary knowledge including material, engineering, and cell biology. Advantages of using SD-TEVGs as compared to autografts, include noninvasive surgery during preparation of grafts, unlimited availability, and customized dimension.

small-diameter tissue engineered vascular grafts (SD-TEVGs) large-animal models patency end-to-side anastomosis end-to-end anastomosis antithrombotic therapy

1. Introduction

The leading cause of death worldwide is cardiovascular disease [1]. In the European Union countries, 119 deaths per 100,000 inhabitants in 2016 were caused by ischemic heart diseases [2]. The latter is most often caused by atherosclerosis, which also results in peripheral artery disease. The involved artery is narrowed in lumen, and the flow rate is limited, resulting in reduced blood perfusion, and oxygen and nutrients supply. Due to the development of improved medication and percutaneous intervention, surgical intervention has decreased in some areas of the world; however, bypass grafting still plays an important role for severely affected patients to recover blood perfusion.

For coronary-artery bypass grafting (CABG), the most optimal graft is autologous left internal mammary artery [3], which offers adequate diameter and length for coronary-artery revascularization [4], with a satisfying long-term patency rate of more than 85% after 10 years [5] (Table 1).

The main failure reason, in the late phase, for left internal mammary artery graft is competitive flow from residual blood flow from the native coronary artery [6]. In contrast, the suboptimal, but most commonly used graft, is saphenous vein that displays a relatively low long-term patency rate of 61% after 10 years [6]. It often fails due to thrombosis in the early phase (within 1 month), whereas intimal hyperplasia and atherosclerosis are the failure reasons in intermediate (within 12 months) and late phases (after 12 months) [7]. Other autologous arteries (e.g.,

radial artery and right gastroepiploic artery) may be used alternatively for CABG; however, no prosthetic graft is approved for CABG yet [4].

For bypass grafting in lower extremity, infrainguinal bypass above the knee (femoropopliteal bypass) is considered to be a medium-diameter surgery, while infrainguinal bypass below the knee (femorodistal bypass) is considered to be a small-diameter bypass surgery (Table 1). Although the autologous saphenous vein displays a diameter usually smaller than 6 mm, it still remains the most optimal graft for both above- and below-knee bypass surgery due to the unavailability of autologous arterial graft in general [8], but it should be noted that the primary patency rate is 53.7% after 3 years [9]. Mechanisms of saphenous vein graft failure in infrainguinal bypass are suggested to be similar to those in CABG [10]. However, unlike CABG, other non-autologous grafts (e.g., prosthetic grafts and human umbilical veins) are available for lower extremity bypass grafting above the knee with relative lower, but still comparable, primary patency rates [8]. Small-diameter bypass grafting is also performed in upper extremity but with much less incidence than bypass grafting in the heart and the lower extremities [11].

In general, arterial bypass grafting in the heart or below the knee requires small-diameter grafts. Thus, shortage of material for such surgeries remains a big challenge because autologous grafts are often not available in certain patient groups such as claudicants, patients with diabetics or vein disease, and in patients requiring reoperations. This has further underscored the need for developing alternative small-diameter vascular grafts [12][13]. One candidate, small-diameter tissue-engineered vascular grafts (SD-TEVGs), is fabricated using novel techniques and interdisciplinary knowledge including material, engineering, and cell biology. Advantages of using SD-TEVGs as compared to autografts, include noninvasive surgery during preparation of grafts, unlimited availability, and customized dimension.

Table 1. Medium- and small-diameter arterial bypass grafting in clinical practice.

Diseases	Bypass Site	Host Artery Diameter (mm)	Optimal Graft	Graft Length (cm)	Graft Diameter (mm)	Anastomotic Configuration (Distal)	1-Year Patency	3-Year Patency	10-Year Patency
Coronary-artery disease (CAD)	Coronary-artery bypass	P: 1.6–7.2 M: 1.0–6.7 D: 0.8–2.5 * [4]	Left internal mammary artery [3]	14.3–19.5 [4]	1.5–1.8 [4]	End-to-side	95% [5]	93% [5]	85% [5]

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Peripheral arterial disease (PAD)	Infrainguinal bypass	Femoral: P: 10.2 D: 7.7 Popliteal: 6.9 Tibial: 3.8/4.2 # [14]	Great saphenous vein [15]	72.4 ± 6.6 [16]	P: 5.2 ± 0.6 M: 3.3 ± 0.5 D: 1.7 ± 0.3 [16]	End-to-side	74.4% [9]	53.7% [9]	

* P: proximal segment; M: media segment; D: distal segment; and # Tibial: anterior/posterior.

2. SD-TEVGs Evaluated in Humans

In previous studies, several types of SD-TEVGs have undergone preclinical evaluation, such as arterial bypass grafts or arteriovenous shunts. To exemplify current progress, representative SD-TEVGs tested in humans are summarized in Table 2 and below.

There are several case reports and clinical trials that investigated the usage of synthetic SD-TEVGs at the aortocoronary site.

In 1976, Sauvage et al. reported about a knitted Dacron filamentous vascular prosthesis (3.5 mm in diameter and 4 cm long) as an interposition graft at the aortocoronary site in a 65-year-old patient to repair the coronary artery after removal of a saccular aneurysm in the ascending aorta [17]. This graft maintained patency during the 16-month follow-up period. Success has also been observed in similar synthetic grafts at the aortocoronary site [18]. However, considering the bypass location between the aorta and the proximal end of the coronary artery with high flow, these case reports did not support implantation of synthetic graft for common CABG, where the grafts need to be implanted to coronary arteries at more distal positions [17].

From 1988 to 2003, at least six types of grafts were further evaluated in patients that underwent CABG [19] (Table 2):

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(1) glutaraldehyde-fixed bovine internal thoracic artery grafts with a patency of 46% after 3–13-month follow-up published in 1982 [20];

(2) cryopreserved allograft saphenous vein with a patency of 41% after 2–16-month follow-up published in 1992 [21];

(3) dialdehyde starch-treated bovine internal thoracic artery grafts with a patency of 16% after 3–23-month follow-up in 1993 [22];

(4) N-acetylated bovine internal mammary artery with a patency of 57% after 1–4.5-year follow-up in a study in 2004 [23] and a patency of 23% after 8–11-month follow-up in another study in 2008 [24];

(5) autologous endothelial cell-seeded expanded polytetrafluoroethylene (ePTFE) grafts with a patency of 90.5% after 7.5–48-month follow-up in 2000 [25];

(6) de-endothelialized and cryopreserved allograft veins seeded by autologous endothelial cells with a patency of 50% after 9-month follow-up published in 2001 [26] and 0% patency after 32 months, published in 2019 [27].

The first four types of grafts showed very poor patency and therefore were not recommended as alternative choices for CABG in patients, whereas the fifth type of graft displayed high patency [25], suggesting promising improvement of graft patency by endothelialization as also discussed below. This improvement of endothelialization was also seen in the allograft veins seeded by autologous endothelial cells [26][27], as compared to the similar cryopreserved allograft saphenous vein but without endothelialization [26]. However, when comparing the two types of grafts that were both endothelialized [25][26][27], the synthetic ePTFE [25] seems much better than the cryopreserved allograft [26][27], indicating that elimination of immunogenicity in the allografts cannot be fully achieved by cryopreservation and therefore need to be further improved by using other methodology such as decellularization. Thus, until now, modified synthetic, allogeneic, or xenogeneic grafts have indeed been studied in humans for CABG, however with very limited success due to their thrombogenicity. Furthermore, there are no human studies testing SD-TEVGs for CABG initiated after 2008.

In regard to human studies for artery bypass grafting below the knee, Almasri et al. reviewed large-scale clinical trials in 2018 and revealed a primary patency around 50% of FDA-approved prosthetic grafts (cryopreserved saphenous vein allografts and heparin bounded polytetrafluoroethylene (PTFE)) at 1-year follow-up using meta-analysis [28]. Recently, another type of FDA-approved TEVG termed crosslinked bovine carotid artery graft (BCAG) has been examined in patients for artery bypass grafting below the knee. They display a long-term primary patency at 50–75% 3 years after implantation (Table 2) [29], which is comparable to autologous vein graft and might be better than synthetic grafts [28]. However, the study was retrospective, and therefore, prospective, randomized studies are needed to compare these xenogeneic grafts with autologous vein grafts and synthetic grafts. To reduce the thrombogenicity of synthetic grafts, Williams et al. recellularized ePTFE with autologous adipose-derived

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stromal vascular fraction cells and implanted them in ePTFE grafts as femorotibial bypass grafts in a phase 1 clinical trial (Table 2) [30]. The 1-year patency of these cellularized grafts was 60% (3/5 were patent).

Table 2. Small-diameter tissue-engineered vascular grafts (SD-TEVGs) evaluated in humans.

Author	Graft Type	Year	Graft	Number of Patients	Recellularization	Follow-Up Time	Primary Patency
			CABG				
Silver [20]	Allogeneic	1982	Glutaraldehyde-fixed human umbilical vein grafts	11	None	3 to 13 months	46%
Laub [21]	Allogeneic	1992	Cryopreserved allograft saphenous vein	19	None	2 to 16 months	41%
Mitchell [22]	Xenogeneic	1993	Dialdehyde starch-treated bovine internal mammary artery	18	None	3 to 23 months	16%
Reddy [23]	Xenogeneic	2004	No-React bovine internal mammary artery	7	None	1 to 4.5 years	57%
Englberger [24]	Xenogeneic	2008	No-React bovine internal mammary artery	17	None	3 to 11 months	23%
Laube [25]	Autologous cells on synthetic	2000	Autologous endothelial cell-seeded ePTFE graft	14	Autologous endothelial cell	7.5 to 48 months	91%
Lamm [26] and Herrmann [27]	Autologous cells on allograft	2001 and 2019	Deendothelialized/cryopreserved allograft veins seeded by autologous endothelial cells	12	Autologous endothelial cell	16 to 18 years	80% (6 months); 50% (9 months); 0% (32 months)
			Bypass grafting below knee				
Lindsey [29]	Xenogeneic	2017	Crosslinked bovine carotid artery	80	None	5 years	52% to 75%
Williams [30]	Autologous cells on synthetic	2017	Adipose-Derived Stromal Vascular Fraction Cell seeded ePTFE	5	Adipose-Derived Stromal Vascular Fraction Cell	1 year	60%
			AV shunt for hemodialysis access				
Kennealey [31]	Xenogeneic	2011	Crosslinked bovine carotid artery	26	None	1 year	61%

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Author	Graft Type	Year	Graft	Number of Patients	Recellularization	Follow-Up Time	Primary Patency
Harlander-Locke [32]	Xenogeneic	2014	Crosslinked bovine carotid artery	17	None	18 months	73%
Wystrychowski [33]	Allogeneic	2014	Allogeneic cell sheet-based TEVG, dehydrated	3	None	<11 months	9.5 patient-month of use
Lawson [34]	Allogeneic	2016	Allogeneic human acellular vessels	60	None	>1 year	28% at 12 months
L'Heureux [35]	Autologous	2007	Autologous cell sheet-based TEVG	6	Autologous fibroblast and endothelial cells	<13 months	24 patient-months of use
McAllister [36]	Autologous	2009	Autologous cell sheet-based TEVG	10	Autologous fibroblast and endothelial cells	>6 months	68 patient-months of use
Wystrychowski [37]	Autologous	2011	Autologous cell sheet-based TEVG, cold-preserved	1	Autologous endothelial cells	8 weeks	8 patient-weeks of use

SD-TEVGs: Small-diameter tissue engineered vascular grafts; CABG: coronary-artery bypass grafting; AV shunt: arteriovenous shunt. There might be other similar studies not included here.

of the cell-sheet-based TEVGs was found fairly positive, at 89% after more than 1 year follow-up. Moreover, as compared to the synthetic grafts tested, the cell-sheet-based TEVGs possessed higher resistance to prosthetic infection, which is a common reason for graft failure in arteriovenous shunt for hemodialysis access [34]. Crosslinked BCAG has also been suggested as an alternative to autologous grafts. When implanted in patients as arteriovenous shunt for hemodialysis access, crosslinked BCAG exhibit a patency of 60% to 70% after 12 or 18 months [31][32], which is similar to the positive outcome observed in lower extremity bypass grafting [29].

Thus, although some progress has been achieved regarding SD-TEVGs in clinical studies, autologous arteries or veins are still superior and the first choice for small-diameter artery bypass grafting. However, techniques in this field develop at a high speed (see below), and progress is substantiated by the large number of studies testing SD-TEVGs in large animals.