Late-term results of tissue-engineered vascular grafts in humans

Narutoshi Hibino, MD, PhD,^a Edward McGillicuddy, MD,^a Goki Matsumura, MD, PhD,^b Yuki Ichihara, MD,^b Yuji Naito, MD, PhD,^a Christopher Breuer, MD,^a and Toshiharu Shinoka, MD, PhD^a

Objective: The development of a tissue-engineered vascular graft with the ability to grow and remodel holds promise for advancing cardiac surgery. In 2001, we began a human trial evaluating these grafts in patients with single ventricle physiology. We report the late clinical and radiologic surveillance of a patient cohort that underwent implantation of tissue-engineered vascular grafts as extracardiac cavopulmonary conduits.

Methods: Autologous bone marrow was obtained and the mononuclear cell component was collected. Mononuclear cells were seeded onto a biodegradable scaffold composed of polyglycolic acid and ϵ -caprolactone/L-lactide and implanted as extracardiac cavopulmonary conduits in patients with single ventricle physiology. Patients were followed up by postoperative clinic visits and by telephone. Additionally, ultrasonography, angiography, computed tomography, and magnetic resonance imaging were used for postoperative graft surveillance.

Results: Twenty-five grafts were implanted (median patient age, 5.5 years). There was no graft-related mortality (mean follow-up, 5.8 years). There was no evidence of aneurysm formation, graft rupture, graft infection, or ectopic calcification. One patient had a partial mural thrombosis that was successfully treated with warfarin. Four patients had graft stenosis and underwent successful percutaneous angioplasty.

Conclusion: Tissue-engineered vascular grafts can be used as conduits in patients with single ventricle physiology. Graft stenosis is the primary mode of graft failure. Further follow-up and investigation for the mechanism of stenosis are warranted. (*J Thorac Cardiovasc Surg* 2010;139:431-6)

Supplemental material is available online.

Approximately 1% of all live births are affected by congenital heart disease, and each year approximately 10,000 children undergo reconstructive operations to repair complex congenital abnormalities.¹ Currently used prosthetic materials, such as polytetrafluoroethylene, lack growth potential and are prone to thrombosis and infection. Additionally, prosthetic materials are nonviable and do not possess the ability to grow.

Through tissue engineering, it is feasible to construct a vascular graft that has structural and biochemical characteristics similar to those of a native vessel.² By use of the classic tissue-engineering paradigm, an individual's own

cells can be seeded onto a biodegradable scaffold, with the scaffold providing a source of cell attachment and early structural integrity.³ As the scaffold degrades, vascular neo-tissue forms and a living, biocompatible conduit is created.

We⁴ have previously reported the satisfactory short-term results of a human trial in which tissue-engineered vascular grafts (TEVGs) were implanted as extracardiac total cavopulmonary connections (TCPCs) in 25 patients with single ventricle physiology. In this study, we report the long-term clinical and radiologic surveillance of the patient cohort that underwent implantation of TEVGs as extracardiac TCPCs. Several imaging modalities, including angiography, computed tomography (CT), magnetic resonance imaging (MRI) angiography, and transthoracic ultrasonography, were used to assess TEVG patency and morphology.

MATERIAL AND METHODS

Scaffold Fabrication

A hybrid tubular scaffold composed of a woven fabric of polyglycolic acid and ϵ -caprolactone or L-lactide was constructed as previously described.⁴ On the basis of vessel size and hemodynamics, the appropriate diameter scaffold was selected (range, 12–24 mm). The scaffolds were 0.6 to 0.7 mm in thickness and 13 cm in length. The length of the scaffold was modified by the surgical team as necessary to accommodate each patient's anatomy.

Cell Collection and Scaffold Preparation

As described previously,⁴ with the patient under general anesthesia and before median sternotomy for the definitive operation, bone marrow (5 mL/kg body weight) was aspirated from the anterosuperior iliac spine. The mononuclear cell component of the marrow ($2.26 \pm 1.02 \times 10^8$ cells)

From Yale University School of Medicine,^a Section of Cardiac Surgery, New Haven, Conn; and Tokyo Women's Medical University,^b Tokyo, Japan.

Disclosures: R. Shinoka and C. Breuer report grant support from Gunze, Ltd, the manufacturer of the scaffold used in this study.

Funded by the Doris Duke Charitable Foundation.

Read at the Eighty-ninth Annual Meeting of The American Association for Thoracic Surgery, Boston, Mass, May 9–13, 2009.

Received for publication April 30, 2009; revisions received Sept 14, 2009; accepted for publication Sept 29, 2009.

Address for reprints: Narutoshi Hibino, MD, PhD, Yale School of Medicine, Section of Cardiac Surgery, 333 Cedar St, Boardman 204, PO Box 208039, New Haven, CT 06520 (E-mail: narutoshi.hibino@yale.edu).

0022-5223/\$36.00

Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery
doi:10.1016/j.jtcvs.2009.09.057

Abbreviations and Acronyms

CT	= computed tomography
MRI	= magnetic resonance imaging
TCPC	= total cavopulmonary connection
TEVG	= tissue-engineered vascular graft

was collected with Histopaque-1077 (Sigma Chemical Co, St Louis, Mo) centrifugation, and these cells were seeded onto the scaffold by manual pipetting. The seeded scaffold was incubated in diluted autologous plasma for 2 hours before implantation.

Surgical Implantation

In 2001, the ethics committee at Tokyo Women's Medical University approved the implantation of TEVGs in human subjects. The following inclusion criteria were used for patient screening: elective surgery, age younger than 30 years, full understanding of the procedure by the patient or family, and minimal extracardiac disease burden. Informed consent was obtained from each patient, or from the parent/guardian if the patient was a minor, before proceeding. Between September 2001 and December 2004, 25 patients underwent an extracardiac TCPC using a TEVG (Table E1). The median patient age at the time of TEVG implantation was 5.5 years (range 1–24 years). The mean patient body weight at the time of TEVG implantation was 19.5 kg (range 7.5–51.6 kg). The patients who had small grafts (patients 17 and 19) had an azygos connection. Anticoagulation therapy with warfarin sodium and aspirin was started 2 days postoperatively and continued for 3 to 6 months. Patients were monitored radiographically with transthoracic echocardiography, multislice CT, cineangiography, or MRI angiography. Patients were followed up postoperatively in a multidisciplinary clinic. Additionally, all patients were contacted by telephone to confirm their most recent clinical status.

RESULTS

Early Trial Results

We defined early results as clinical and radiographic events within 30 days of patient discharge after TEVG implantation. At this point, all patients were alive and free of symptoms. Postoperative angiography, ultrasonography, or CT demonstrated that all TEVGs were patent and there was no evidence of stenosis, thrombosis, or aneurysmal dilation of the TEVG.

Trial Results 1 Year After Implantation

Patients continued to be monitored with angiography, ultrasonography, MRI angiography, or CT (Figure E1). Partial mural thrombosis in 1 patient was successfully treated with warfarin anticoagulation (Figure E2). A patient with hypoplastic left heart syndrome died 6 months after TEVG implantation of congestive heart failure resulting from severe tricuspid regurgitation (Table 1).

Most Recent Follow-up

There was no graft-related mortality during the follow-up period (range, 4.3–7.3 years; mean, 5.8 years). All patients underwent a catheterization-based angiographic study, CT,

or MRI. There was no evidence of aneurysm formation, graft rupture, or ectopic calcification in any graft interrogated with any imaging modality (Figure 1). Of note, 1 patient had a hemiazygos connection, and a 12-mm diameter TEVG was implanted; this graft was patent as demonstrated by postoperative imaging. In addition to the patient noted above in the 1-year analysis, 3 other patients died after TEVG implantation: A patient with tricuspid atresia died of complications related to subarachnoid hemorrhage 4 years after TEVG implantation; a second patient, with a known coronary artery anomaly diagnosed on cardiac catheterization, died suddenly 4 years postoperatively; a third patient, who had subaortic stenosis, died suddenly 2 years after graft implantation. Significantly, surveillance imaging in the months before all 4 patient deaths (including the patient who died during the midterm analysis) demonstrated a patent TEVG. Six (24%) patients had asymptomatic graft narrowing noted on routine surveillance imaging. Four of 6 patients underwent successful balloon angioplasty (Figure 2), including 1 patient who required repeat balloon angioplasty and stent placement in the stenosed segment of the TEVG (Table 2).

Postoperative Functional Status

Surviving subjects were contacted by telephone in January 2009 to determine their current functional status. All contacted patients were attending school or work regularly. Seventeen (81%) patients were in New York Heart Association functional class I and 3 patients were in functional class II. Eight patients (40%) were not receiving any daily medications (Table 3).

DISCUSSION

Inasmuch as the prosthetic material used as conduits in surgery for congenital heart disease lacks growth potential, surgical reintervention is often necessary.^{5,6} Additionally, synthetic grafts are at risk for thrombosis or infection. In an effort to overcome these limitations, we have applied tissue-engineering technology to the field of cardiac surgery. On the basis of several initial animal experiments,^{2,7-10} we have previously reported the successful implantation of TEVGs in humans (average follow-up, 1.3 years). In an effort to better characterize graft morbidity and mortality, we continued to monitor our surgical population clinically and radiographically. Our mean follow-up is now 5.8 years, and to this point no graft-related deaths have occurred. In a patient population that often has severe cardiovascular compromise, with a concomitantly shortened life expectancy, our data suggest that TEVGs are technically feasible.

One of the chief advantages of tissue engineering is the potential to create autologous tissue, obviating the need for antiplatelet, anticoagulant, or immunosuppressive therapy. In this study, anticoagulation and antiplatelet agents were

TABLE 1. Patient status 1 year after TEVG implantation

Patient	Age at operation (y)	Graft type	Graft size (cm)	Patient status	Graft status	Graft patency	Graft-related complications
1	2	PLA	16	Alive	Intact	Patent	None
2	1	PLA	20	Alive	Intact	Patent	None
3	7	PLA 1	8	Alive	Intact	Patent	None
4	21	PLA	24	Alive	Intact	Patent	None
5	4	PLA	20	Alive	Intact	Patent	None
6	12	PLA	24	Alive	Intact	Patent	None
7	17	PLA	24	Alive	Intact	Patent	None
8	19	PLA	22	Alive	Intact	Patent	None
9	3	PLA	12	Alive	Intact	Patent	None
10	2	PLA	16	Dead	Intact	Patent	None
11	2	PGA	16	Alive	Intact	Patent	None
12	13	PLA	20	Alive	Intact	Patent	None
13	2	PGA	16	Alive	Intact	Patent	Thrombosis
14	2	PGA	18	Alive	Intact	Patent	None
15	2	PGA	12	Alive	Intact	Patent	None
16	2	PGA	16	Alive	Intact	Patent	None
17	24	PGA	18	Alive	Intact	Patent	None
18	1	PGA	16	Alive	Intact	Patent	None
19	11	PGA	18	Alive	Intact	Patent	None
20	2	PGA	16	Alive	Intact	Patent	None
21	3	PGA	16	Alive	Intact	Patent	None
22	4	PGA	18	Alive	Intact	Patent	None
23	4	PGA	18	Alive	Intact	Patent	None
24	13	PGA	16	Alive	Intact	Patent	None
25	2	PGA	18	Alive	Intact	Patent	None

TEVG, Tissue-engineered vascular graft; PLA, poly-L-lactic acid; PGA, Polyglycolic acid.

discontinued 6 months postoperatively in all patients with no evidence of graft thrombosis (96%). In the long term, 40% of patients remained free of any daily medications, which improves quality of life and decreases the incidence of medication-related complications and comorbidities. In contrast, in studies investigating artificial graft materials such as Dacron or polytetrafluoroethylene, most subjects received long-term oral anticoagulation with warfarin or antiplatelet therapy with aspirin.¹¹⁻¹³

The remodeling of TEVGs and the mechanisms of vascular neotissue formation remain a most compelling and

intensely studied subject. In this study, surveillance imaging revealed graft stenoses in 6 (24%) patients. This stenosis rate was greater than in those studies investigating artificial graft material.¹¹⁻¹³ Graft stenosis, however, is frequently asymptomatic, leading to significant underreporting.¹⁴ When serially imaged with MRI, all synthetic grafts have some degree of stenosis within 6 months of implantation, with a mean 18% reduction in diameter and a maximum reduction of 32%.¹¹ These finding were confirmed in a second study evaluating extracardiac TCPC graft morphology using angiography.¹⁵ Graft narrowing tended to stabilize after this

FIGURE 1. TEVG angiography, 5 years after implantation (A) and 4 years after implantation (B). There was no stenosis, aneurysm formation, or ectopic calcification in these TEVGs.

FIGURE 2. Four patients (A–D) with TEVG stenosis underwent successful balloon angioplasty. *PTA*, Percutaneous transluminal angioplasty.

initial period, but the use of angioplasty and stenting is described in many series.^{11,16} Additionally, the degree of stenosis is difficult to estimate based on a variety of variables, including the change of shape of a conduit from a circular cross section to an oval cross section that often occurs. Also, the 3-dimensional nature of vascular grafts limits accurate size and boundary detection with 2-dimensional modalities such as angiography.¹⁵ Finally, indications for the therapy of asymptomatic stenosis are not standardized,

leading to significant variability in the use of angioplasty, stenting, and graft replacement.

The limitations of this study must be acknowledged. Although this trial represents the first use of tissue-engineered conduits in humans, the number of study subjects was relatively small and only a single institution was involved. Furthermore, a standard radiologic surveillance protocol was not adhered to. Finally, this study was not randomized with matched controls. Currently, we are applying to the

TABLE 2. Patient late-term status after TEVG implantation

Patient	Age at operation	Graft type	Graft size (cm)	Patient status	Graft status	Graft patency	Graft-related complications
1	2	PLA	16	Alive	Intact	Patent	None
2	1	PLA	20	Alive	Intact	Patent	None
3	7	PLA	18	Alive	Intact	Patent	Stenosis*
4	21	PLA	24	Alive	Intact	Patent	None
5	4	PLA	20	Alive	Intact	Patent	None
6	12	PLA	24	Alive	Intact	Patent	None
7	17	PLA	24	Alive	Intact	Patent	None
8	19	PLA	22	Dead	Intact	Patent	None
9	3	PLA	12	Alive	Intact	Patent	Stenosis*
10	2	PLA	16	Dead	Intact	Patent	None
11	2	PLA	20	Dead	Intact	Patent	None
12	13	PGA	16	Alive	Intact	Patent	Stenosis*
13	2	PGA	16	Alive	Intact	Patent	Thrombosis
14	2	PGA	18	Alive	Intact	Patent	None
15	2	PGA	12	Alive	Intact	Patent	None
16	2	PGA	16	Alive	Intact	Patent	None
17	24	PGA	18	Alive	Intact	Patent	None
18	1	PGA	16	Alive	Intact	Patent	Stenosis*
19	11	PGA	18	Alive	Intact	Patent	None
20	2	PGA	16	Alive	Intact	Patent	None
21	3	PGA	16	Alive	Intact	Patent	None
22	4	PGA	18	Alive	Intact	Patent	None
23	4	PGA	18	Alive	Intact	Patent	None
24	13	PGA	16	Alive	Intact	Patent	None
25	2	PGA	18	Dead	Intact	Patent	None

TEVG, Tissue-engineered vascular graft; PLA, poly-L-lactic acid; PGA, Polyglycolic acid. *This patient underwent successful angioplasty.

TABLE 3. Summary of the results of TEVG telephone survey

Patient	Telephone contact	Patient status	NYHA class	Attends school/(work)	Participates in gym/(athletics)	Reported body weight (weight at surgery)
1	Yes	Alive & well	I	Yes	Yes	27 kg (11 kg)
2	Yes	Alive & well	I	Yes	Yes	24 kg (8 kg)
3	Yes	Alive & well	II	Yes	No	23 kg (19 kg)
4	Yes	Alive & well	I	Yes	Yes	47 kg (44 kg)
5	Yes	Alive & well	I	Yes	Yes	32 kg (14 kg)
6	Yes	Alive & well	I	Yes	Yes	53 kg (37 kg)
7	Yes	Alive & well	II	Yes	No	54 kg (47 kg)
8	N/A	dead	N/A	N/A	N/A	N/A
9	Yes	Alive & well	I	Yes	Yes	29 kg (14 kg)
10	N/A	dead	N/A	N/A	N/A	N/A
11	Yes	Alive & well	I	Yes	Yes	24 kg (11 kg)
12	Yes	dead	N/A	N/A	N/A	N/A
13	Yes	Alive & well	I	Yes	Yes	21 kg (10 kg)
14	Yes	Alive & well	II	Yes	No	22 kg (9 kg)
15	Yes	Alive & well	I	Yes	Yes	24 kg (11 kg)
16	Yes	Alive & well	I	Yes	Yes	19 kg (9 kg)
17	Yes	Alive & well	I	Yes	Yes	55 kg (52 kg)
18	Yes	Alive & well	I	Yes	Yes	20 kg (9 kg)
19	Yes	Alive & well	I	Yes	Yes	54 kg (26 kg)
20	Yes	Alive & well	I	Yes	Yes	22 kg (11 kg)
21	Yes	Alive & well	I	Yes	Yes	15 kg (11 kg)
22	Yes	Alive & well	I	Yes	Yes	22 kg (13 kg)
23	No	N/A	N/A	N/A	N/A	N/A
24	Yes	Alive & well	I	Yes	Yes	43 kg (26 kg)
25	No	Dead	N/A	N/A	N/A	N/A

TEVG, Tissue-engineered vascular graft; NYHA, New York Heart Association; N/A, not available.

United States Food and Drug Administration and our institutional review board for permission to implant TEVGs in humans with single ventricle physiology.

In conclusion, this trial demonstrates the feasibility of using tissue-engineering technology to create vascular grafts for use as extracardiac TCPCs. Inasmuch as stenosis is the primary mode of graft failure on TEVGs, further follow-up and investigation for the mechanism of stenosis are warranted. Continued study regarding the mechanisms of TEVG stenosis will allow us to generate the next generation of TEVGs.

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Discussion

Dr John Edmund Mayer, Jr (Boston, Mass). You have some patients who have not survived long term in your tissue-engineered extracardiac Fontan group. Do you have any histologic studies on those explanted grafts from autopsies?

Dr Hibino. Unfortunately, for these TCPC graft-implanted patients, the families declined autopsies; therefore, we do not have the histologic information. We have the histologic data, however, from reoperation patients. In these patients we used a tissue engineered graft as a patch for pulmonary angioplasty in a stenosed region. After the angioplasty, pulmonary artery stenosis developed again, including the portion replaced with the TEVG. Here is the histology of the explanted graft at reoperation. In this image we note endothelialization of the tissue and smooth muscle layer formation, which suggests neotissue formation.

FIGURE E1. Three-dimensional CT 1 year after TEVG implantation. The graft is patent and there is no aneurysmal dilation. *Arrows* denote extracardiac TCPC graft.

FIGURE E2. Partial mural thrombus 1 year after TEVG implantation (A, *arrows*) was successfully treated with warfarin anticoagulation (B, *arrows*).

ET/BS

TABLE E1. Patient demographics, diagnoses, and graft type at the time of implantation

Patient	Age (y)	Weight (kg)	Gender	TEVG (PGA/PLA)	Size (mm)	Diagnosis
1	2	11	M	PLA	16	Asplenia, AVSD (A), small RV
2	1	7	M	PLA	20	Asplenia, SRV, DORV, TAPVC (Ib + III)
3	7	18	F	PLA	18	Concordant criss-cross heart, DORV, PAA, MS
4	21	44	F	PLA	24	TA (Ib)
5	4	14	M	PLA	20	SRV, DORV, AVVA
6	12	36	F	PLA	24	Total sinus defect, ASD, TR (III)
7	17	46	M	PLA	24	Asplenia, SLV, CAVVR (III)
8	19	47	F	PLA	22	TA (Ib)
9	3	13	F	PLA	12	Polysplenia, SRV
10	2	7	F	PLA	16	HLHS, MA, IAA (A)
11	2	11	F	PGA	16	Asplenia, SRV, PAA, nonconfluent PA
12	13	23	F	PLA	20	PPA, ASD (II), sinusoidal communication
13	2	9	M	PGA	16	SLV, DILV, Lt AVVA
14	2	9	F	PGA	18	DORV, small LV, VSD, PS, ASD (II)
15	2	11	F	PGA	12	Polysplenia, cAVSD (A), DORV, PS, CAVVR
16	2	8	F	PGA	16	Asplenia, SRV, CAVV, CA, TAPVC (Ib), CAVVR (I)
17	24	51	M	PGA	18	TA (Ia), RA giant thrombosis
18	1	8	M	PGA	16	SRV, DIRV, PA, ASD (II)
19	11	25	M	PGA	18	Asplenia, cAVSD, PS, CAVV, CAVVR (I)
20	2	11	F	PGA	12	Polysplenia, cAVSD, PS, CAVV, CAVVR (I)
21	3	10	F	PGA	16	DORV, VSD, small RA, PLSVC, TAPVC (IIb)
22	4	13	M	PGA	18	PPA, ASD (II), PDA, sinusoidal communication
23	4	14	F	PGA	18	SLV, DILV, PAA, ASD, bilateral SVC
24	13	25	F	PGA	16	Asplenia, SRV
25	2	9	M	PGA	18	TA, SAS

TEVG, Tissue-engineered vascular graft; PGA, Polyglycolic acid; PLA, poly-L-lactic acid; AVSD, atrioventricular septal defect; RV, right ventricle; SRV, single right ventricle; DORV, double-outlet right ventricle; TAPVC, total anomalous pulmonary venous connection; PAA, pulmonary artery atresia; MS, mitral stenosis; TA, tricuspid atresia; AVVA, atrioventricular valve atresia; ASD, atrial septal defect; TR, tricuspid regurgitation; SLV, single left ventricle; CAVVR, common atrioventricular valve regurgitation; SRV, single right ventricle; HLHS, hypoplastic left heart syndrome; MA, mitral atresia; IAA, interruption of aortic arch; PA, pulmonary artery; PPA, pure pulmonary atresia; DILV, double-inlet left ventricle; LV, left ventricle; VSD, ventricular septal defect; PS, pulmonary stenosis; ASD, atrial septal defect; cAVSD, complete atrioventricular septal defect; CAVV, common atrioventricular valve; CA, common atrium; RA, right atrium; PLSVC, persistent left superior vena cava; PDA, patent ductus arteriosus; SVC, superior vena cava; SAS, subaortic stenosis.