Extracardiac total cavopulmonary connection using a tissue-engineered graft

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Objective: Extracardiac and lateral tunnel total cavopulmonary connection are currently 2 major options for patients with a single ventricle physiology. However, each procedure has some disadvantages over the other. We developed a new technique of extracardiac total cavopulmonary connection using a tissue-engineered graft to overcome some of the disadvantages previously associated with both the extracardiac and lateral tunnel procedures.

Methods: Between February 2001 and October 2002, 8 patients underwent an extracardiac total cavopulmonary connection using a tissue-engineered graft in our institution. Collected bone marrow cells (1×10^8 mononucleocytes) from a patient (~ 1 -4 mL/kg body weight) were seeded onto a biodegradable scaffold composed of polycaprolactone-poly(lactic acid) copolymer reinforced with woven poly(lactic acid). After a 2- to 4-hour cultivation, the seeded scaffold was implanted as an extracardiac conduit during the total cavopulmonary connection operation.

Results: There were no hospital or late deaths. At a mean follow-up of 13.4 months (range 4-25 months), all patients are alive and asymptomatic with no need for repeat surgery. A postoperative catheter examination or computed tomography showed all tissue-engineered grafts to be patent and revealed no stenosis, obstruction, or aneurysmal change in the 8 patients.

Conclusion: We believe that extracardiac total cavopulmonary connection using a tissue-engineered graft has the potential to overcome some of the disadvantages previously associated with extracardiac or lateral tunnel total cavopulmonary connection. However, an extended follow-up period is required to clarify the long-term clinical outcome for the tissue-engineered graft.

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Since de Leval and his colleagues introduced the total cavopulmonary connection (TCPC) procedure in 1988, it has been widely performed as a modification of the Fontan operation in patients with a single ventricle physiology.¹ Two major TCPC options are the extracardiac (inferior vena cava [IVC]-right pulmonary artery [PA] conduit) and the lateral tunnel (intra-atrial) procedures.² Outcomes after the Fontan operation have improved markedly in the past 15 years with the use of these 2 procedures.³⁻⁷

TABLE 1. Summary of clinical data for 8 patients undergoing extracardiac total cavopulmonary connection

Patient No.	Heterotaxia	Diagnosis	Age at TCPC (yr)	Prior procedures
1	Polysplenia	AV septal defect	12	Extracardiac TCPC using Hemashield (Boston Scientific Corp, Natick Mass) graft
2	Asplenia	AV septal defect, PAPVD	2	Bilateral MBTs
3	Asplenia	Single RV, TAPVD, pulmonary stenosis	1	Left MBT
4	None	Concordant crisscross heart DORV, pulmonary atresia	7	Left MBT Atrial septectomy
5	None	Tricuspid atresia, pulmonary stenosis	21	Bilateral OBTs central shunt
6	None	Single RV, left AV valve atresia	4	Bidirectional Glenn
7	Asplenia	Single LV, CAVV regurgitation	17	Bidirectional Glenn CAVV plasty
8	Polysplenia	Single RV, CAVV regurgitation, hemiazygos connection	4	TCPS CAVV plasty

TEG diameter (mm)	Concomitant procedures	CPB time (min)	ACC time (min)	Hospital stay (d)
20	Removal of previous Hemashield graft	127	0	139
17	PA angioplasty PAPVD repair	186	0	70
20	TAPVD repair	170	0	46
18	PA angioplasty	105	0	40
24	None	169	0	47
20	PA angioplasty	105	0	30
24	Redo-CAVV plasty	144	110	44
12	Redo-CAVV plasty	93	37	29

Complications	Follow-up period (mo)	Heart rhythm
Pleural effusion	25.6	Sinus
Pleural effusion	18.0	Sinus
None	16.6	Sinus
None	13.7	Sinus
None	11.6	Sinus
None	9.4	Sinus
None	8.4	Sinus
None	4.4	Pacing

ACC, Aortic crossclamp; AV, atrioventricular; CAVV, common atrioventricular valve; CPB, cardiopulmonary bypass; DORV, double-outlet right ventricle; LV, left ventricle; MBT, modified Blalock-Taussig shunt; OBT, original Blalock-Taussig shunt; PA, pulmonary artery; PAPVD, partial anomalous pulmonary venous drainage; PS, pulmonary stenosis; RV, right ventricle; TCPC, total cavopulmonary connection; TCPS, total cavopulmonary shunt; TEG, tissue-engineered graft; TAPVD, total anomalous pulmonary venous drainage.

Each of these procedures, however, has some advantages and disadvantages over the other. Extracardiac TCPC has a lower frequency of late supraventricular arrhythmias in comparison with lateral tunnel TCPC,^{6,7} because no part of the right atrium is exposed to an elevated systemic venous pressure, and because there are no extensive atrial suture lines. In addition, extracardiac TCPC is a technically undemanding procedure when compared with lateral tunnel TCPC in avoiding pulmonary venous obstruction because of the interference of the systemic venous route. On the other hand, extracardiac TCPC requires a prosthetic conduit to connect the IVC to the right PA. However, foreign material (usually polytetrafluoroethylene) has no growth potential. This situation may necessitate a later conduit replacement and increase the risk of conduit thrombosis,^{8,9} although the lateral tunnel could be completed without the use of foreign material.

We applied a tissue-engineered graft (TEG) during an extracardiac TCPC operation to overcome some of the disadvantages that were associated previously with both the extracardiac and lateral tunnel TCPC procedures.

Material and Methods

After having received approval from the ethics committee at Tokyo Women's Medical University, we began the clinical application of TEG. Informed consent was obtained directly from the 21-year-old patient and from the parents of the younger patients. Between February 2001 and October 2002, 8 patients underwent an extracardiac TCPC using a TEG in our institution (Table 1). The mean age at operation was 8.5 years (range 1-21 years), and the mean weight was 22.5 kg (range 9.2-44 kg). The primary diagnosis was asplenia in 3 patients, polysplenia in 2 patients (azygos continuation of the IVC in 1), and normotaxia in 3 patients. The concomitant procedures were as follows: angioplasty of the PA in 3 patients, redo-plasty of the common atrioventricular

Figure 1. Operative field. IVC, inferior vena cava; PA, pulmonary artery; TEG, tissue-engineered graft placed between the IVC and the right PA.

valve in 2 patients, repair of total anomalous pulmonary venous drainage in 1 patient, and repair of partial anomalous pulmonary venous drainage in 1 patient. One patient (patient 8) required DDD pacemaker placement simultaneously because of atrial bigeminy that had been present preoperatively.

The procedures for cell harvesting and cell seeding have been described.¹⁰ Briefly, before a median sternotomy, autologous bone marrow cells (BMCs), approximately 1 to 4 mL/kg body weight, were collected from the anterior superior iliac spine in the operating room. Aspirated BMCs (1×10^8 mononucleocytes) were seeded onto a biodegradable scaffold composed of polycaprolactone-poly(lactic acid) copolymer reinforced with woven poly(lactic acid). This scaffold was designed to degrade by hydrolysis in approximately 3 to 5 years. The seeded scaffold was kept in a culture medium until TCPC anastomosis for approximately 2 to 4 hours at 37°C in 100% humidity and a 5% CO₂ atmosphere.

The operation was performed by conventional cardiopulmonary bypass with ascending aortic perfusion and direct bicaval (or tricaval, when necessary) venous drainage. Previous systemic to pulmonary shunts, if present, were taken down immediately after bypass onset. TCPC anastomosis using a TEG was performed under total bypass with a beating heart in all patients except for 2 in whom atrioventricular valve plasty was required. The superior vena cava was anastomosed to the upper surface of the right PA in an end-to-side fashion. The IVC was clamped and transected at the inferior cavoatrial junction. A TEG selected according to the orifice size of the IVC was sutured to the IVC in an end-to-end manner. The caudal aspect of the central PA was opened widely, after which the other end of the TEG was sutured to the PA with a conduit offset a few millimeters toward the proximal PA (Figure 1). Anastomosis between the TEG and the native tissue was performed using absorbable PDS running suture (Ethicon Inc, Summerville, NJ), except in patients 5 (21 years old) and 7 (17 years old). Anticoagulation therapy with warfarin sodium and aspirin was continued until 6 months after operation. Thereafter, anticoagulation therapy with aspirin alone was continued for 12 months postoperatively.

Results

The diameter of the TEG was 17 mm in 1 patient, 18 mm in 1 patient, 20 mm in 3 patients, 24 mm in 2 patients, and 12 mm in 1 patient with azygos continuation (Table 1). The mean cardiopulmonary bypass time was 137 ± 35 minutes. No patients required fenestration in this series.

There were no hospital deaths, and the mean hospital stay was 55.6 days (range 29-127 days). At a mean follow-up of 13.4 months (range 4-25 months), all patients are alive and asymptomatic with no need for repeat surgery. A postoperative catheter examination (in 4 patients), computed tomography (in 2 patients), or magnetic resonance imaging (in 2 patients) showed all TEGs to be patent and revealed no stenosis, obstruction, thrombotic complications, or aneurysmal change in any of the 8 patients (Figure 2). Sinus rhythm was maintained in 7 patients, and pacing rhythm was observed in 1 patient who required DDD pacemaker (Medtronic, Inc, Shoreview, Minn) implantation. No atrial dysrhythmias were identified by a routine electrocardiographic examination at our outpatient unit.

Discussion

One of the important features of our technique is that the scaffold used here is designed to disappear in 3 to 5 years after the TCPC operation. Thus, the whole structure of the conduit connecting the IVC to the PA should be replaced by autologous tissue, and the permanent presence of foreign material can be avoided. In light of these characteristics, the theoretic advantages of the TEG that we used here are its growth potential, low degree of thrombogenicity and calcification, and great resistance to infection. The age of patients undergoing the TCPC operation is currently trending much younger because of the consensus that cyanosis should be corrected in the early years. The younger the patients with TCPC are, the greater will be their somatic growth, making the benefits of the TEG significant.

Azygos or hemiazygos continuation is a difficult situation in TCPC surgery for patients with heterotaxia syndrome. Because blood flow from the hepatic vein is lower than that of the normal IVC, the risk of conduit thrombosis may be higher.⁹ A TEG, even in this situation, would have better long-term patency than polytetrafluoroethylene because a TEG has the potential for remodeling into appropriate dimensions according to blood flow through the conduit.

For the first patient in this series, cells were isolated from the saphenous vein wall and cultured to make the TEG as we previously reported.¹¹⁻¹³ However, general anesthesia was mandatory to isolate the cells in children, and a 3-week cell culture was required to construct the TEG. As a result, we used autologous BMCs as a cell source in all other patients, because they contained multipotential cells capable of differentiating into several different tissue types.¹⁴⁻¹⁶ In

Figure 2. Angiograms of the TEG 6 months after undergoing an extracardiac total cavopulmonary connection (TCPC) operation in patient 2 (A), 4 months after TCPC in patient 3 (B), 1 month after TCPC in patient 4 (C), and 8 months after TCPC in patient 6 (D). Note that smooth surface of the TEG and well-enhanced PAs.

addition, the collection of BMCs could be performed on the same day as the operation, which thus rendered it unnecessary for hospital admission before the TCPC operation.

Anticoagulation therapy after the extracardiac TCPC operation remains controversial. From our experimental data on dogs, endothelialization of the inner surface of the TEG was observed at 1 to 3 months after TEG implantation.¹² Therefore, patients who had a TEG implanted in this series received anticoagulation therapy with both warfarin sodium and aspirin for 6 months after surgery and with aspirin alone for 6 months thereafter.

Conclusion

We believe that extracardiac TCPC with a TEG has the potential to overcome the disadvantages associated with

previous extracardiac or lateral tunnel TCPC. However, an extended follow-up period is still required to clarify the long-term clinical outcome for TEGs.

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