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Bovine Mesenteric Venous Graft as an Alternative Conduit in Patients with Cyanotic Heart Disease with E-Polytetrafluoroethylene Graft Failure Caused by Thrombophilic Factor Positivity after Modified Blalock-Taussig Shunt

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ABSTRACT

Modified Blalock-Taussig shunt (MBTS) is a palliative operation for cyanotic congenital heart disease (CCHD) in patients for whom total correction is not appropriate. Many synthetic or biologic grafts have been proposed as alternative shunt materials. The use of a bovine mesenteric venous graft (BMVG) as a systemic-to–pulmonary artery shunt conduit without the administration of antiaggregant and anticoagulant has been proposed as a treatment for neonates with CCHD, but few reports address the importance of thrombophilic risk factors in MBTS and bovine venous graft as a shunt material. We used BMVG as a shunt material without any antiaggregant or antiplatelet regimen in 13 patients with CCHD, all of whom were candidates for MBTS and had thrombophilic risk factors assessed in our initial study. Early shunt failure occurred in the first 3 patients and was attributed to less surgical experience with this graft. No complications were attributable to graft material or surgery itself. In all cases functioning MBTSs were observed on follow-up. Our study results show that thrombophilic factors should be evaluated before the MBTS procedure. BMVG could be the choice of graft for use without the administration of antiaggregant and anticoagulants in patients with thrombophilic risk factors.

INTRODUCTION

Systemic-to-pulmonary shunts have proven to be highly effective for the palliation of patients with cyanotic congenital heart disease (CCHD) who are not candidates for early complete repair. These shunts usually allow adequate oxygen saturation and pulmonary artery growth until definitive correction can be performed. Some patients, however, may become critically cyanotic before the optimal time for staging or definitive repair, and very rarely, interstage sudden death due to shunt occlusion may occur [Fenton 2003]. Several authors have documented the presence of stenosis in modified Blalock-Taussig shunts at the time of takedown because of different causes such as graft kinking or calcification of the synthetic graft [Tsai 1996; Bove 1997; Malm 1998; Tomizawa 1998; Fenton 2003].

Because these previous reports did not include investigation of thrombophilic risk factors for graft occlusion during the postoperative period, we evaluated thrombophilic factors, including factor II, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, factor XII, protein C, protein S, von Willebrand factor, antithrombin III, factor V Leiden, prothrombin G20210A mutation, activated protein C resistance, and homocysteine to assess the patency of E-polytetrafluoroethylene (ePTFE)-constructed MBTS in patients with cyanotic congenital heart defects (CCHD).

In an initial study (first results presented at the 54th International Congress of The European Society for Cardiovascular Surgery [Akbulut 2005] we determined thrombophilic risk factors for MBTS. In this initial study, all patients received heparin (activated partial thromboplastin time 60-70 s) and aspirin (5 mg/kg per day) postoperatively. Heparin was continued for 1-3 days. Graft patency was measured with echocardiography after surgery, before discharge, and at 1, 3, and 6 months during follow-up. Mean follow-up time was 9.8 ± 3.6 months. Six patients (16.2%) developed MBTS failure due to thrombosis (group Ia) and 31 did not (group Ib). Mean age of patients was 5.3 ± 4.1 months in group Ia and 3.8 ± 1.7 months in group Ib. There were no statistically significant differences in demographic data between 2 groups, as demonstrated in Table 1, which also shows the primary diagnosis in both groups. Graft failure occurred 2.3 ± 0.8 days after surgery. Levels of factor II, factor VII, factor VIII, and von Willebrand factor were significantly higher in group Ia than in group Ib ($P < .005$). Furthermore, levels of protein C and protein S were significantly lower in group Ia than in group Ib ($P < .005$). Results of thrombophilic factor measurement are shown in Table 2. Calculated cutoff points for factor II, factor VII, factor VIII, and von Willebrand factor were 101.69%, 103.53%, 219.87%, and 180.86%, respectively, and those for protein C

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Table 1. Patient Demographic Data*

	Group Ia (n = 6)	Group Ib (n = 31)	*P*†	Group II (n = 13)	*P*‡
Age, months	5.3 ± 4.1	3.8 ± 1.7	>.05	3.7 ± 1.7	>.05
Male/female, n	3/3	14/17	>.05	6/7	>.05
Weight, kg	2.91 ± 0.14	2.94 ± 0.21	>.05	2.65 ± 0.41	>.05
Graft size, mm	3.83 ± 0.40	4.0 ± 0.44	>.05	4.0 ± 0.0	>.05
Primary diagnosis					
DORV	11	2	—	3	—
TGA	6	1	—	1	—
TOF	11	3	—	4	—
PA	3	0	—	3	—

*DORV indicates double outlet right ventricle; TGA, transposition of great arteries; TOF, tetralogy of Fallot; PA, pulmonary atresia.

†*P* value between group Ia and group Ib;

‡*P* value between group Ia and group II.

and protein S were 59.93% and 70.68%, respectively. Levels of factor II, factor VII, factor VIII, and von Willebrand factor above the documented cutoff points and levels of protein C and protein S below the documented cutoff points were interpreted as risk factors for early graft thrombosis.

Many synthetic or biologic grafts such as PTFE, internal thoracic artery [Cobanoglu 1984], umblical [Leao 1985], and saphenous vein [Tam 2001] have been proposed as alternative sources of shunt material. Despite the number of grafts that have been used, many complications after MBTS operations have been reported. Previously, the bovine mesenteric venous graft (BMVG) has been suggested for hemodialysis access [Katzman 2005] and in bypass procedures for lower limb ischemia [Schmidli 2004]. The use of BMVG without the administration of antiaggregant and anticoagulant administration as a systemic-to–pulmonary artery shunt conduit in neonates was proposed by Kalangos et al [2001]. Therefore, we performed an additional study to investigate the role of thrombophilic factors in MBTS occlusion and the use of a BMVG (ProCol®)-constructed modified Blalock-Taussig shunt.

MATERIALS AND METHODS

Patient Selection

We continued evaluating thrombophilic factors in patients who were candidates for the MBTS procedure. In patients with thrombophilic risk factors we used BMVG to construct the MBTS as described by Kalangos et al [2001]. The study was approved by the ethics committee of our institution, and the parents of all participants gave informed consent. There were 13 patients with 3 or more thrombophilic risk factors, as determined in the initial study (group II). Demographic data

Table 2. Patient Thrombophilic Risk Factors*

	Group Ia (n = 6)	Group Ib (n = 31)	*P*†	Group II (n = 13)	*P*‡
Factor VIII, %	247.6 ± 47.1	177.5 ± 11.7	<.005	251.9 ± 34.5	>.05
Factor IX, %	192.8 ± 80.2	172.3 ± 9.2	>.05	199.6 ± 76.3	>.05
Factor II, %	142.0 ± 79.4	87.7 ± 8.9	>.005	145.2 ± 78.6	>.05
Protein C, %	44.5 ± 17.0	92.9 ± 14.1	>.005	44.9 ± 16.9	>.05
Protein S, %	43.9 ± 24.9	82.2 ± 6.6	>.005	45.8 ± 23.9	>.05
APCR, n	2 (33.3%)	11 (35.4%)	>.05	4 (36.3%)	>.05
Factor V, %	87.2 ± 6.9	84.6 ± 9.2	>.05	86.9 ± 6.8	>.05
Factor VII, %	160.2 ± 84.7	81.5 ± 8.8	>.005	165.0 ± 82.9	>.05
Factor X, %	87.2 ± 6.9	84.9 ± 9.5	>.05	86.9 ± 6.8	>.05
Factor XI, %	91.0 ± 16.7	85.9 ± 10.4	>.05	91.4 ± 16.6	>.05
Factor XII, %	92.2 ± 7.9	84.3 ± 8.3	>.05	92.6 ± 7.8	>.05
AT III, %	86.0 ± 6.7	82.8 ± 7.1	>.05	87.2 ± 5.4	>.05
vWF, %	282.0 ± 58.4	146.3 ± 32.5	>.005	281.3 ± 58.4	>.05
Homocysteine, µg/dL	9.8 ± 3.1	11.1 ± 4.3	>.05	9.6 ± 3.0	>.05
Factor V Leiden, n	2 (33.3%)	5 (16.1%)	>.05	3 (27.2%)	>.05
Prothrombin G20210A mutation, n	1 (16.6%)	2 (6.4%)	>.05	2 (18.1%)	>.05

*APCR indicates activated protein C resistance; AT III, antithrombin III; vWF, von Willebrand factor.

†*P* value between group Ia and group Ib.

‡*P* value between group II and group Ia.

were similar to those patients in the initial study (groups Ia and Ib).

Preparation of BMVG

Before the construction of the MBTS, the Dacron mesh covering the graft was removed, and the BMVG was rinsed in 2 basins, each containing 1 L of saline solution, for a minimum of 5 min and then placed into a third basin containing 500 mL of sterile saline and 20.000 IU heparin for a minimum of 5 min. During this rinsing procedure, the lumen was irrigated with a minimum of 100 mL of the solution with a bulb syringe in the indicated flow direction.

Operative Technique

The operation was performed through a posterolateral thoracotomy in the fourth intercostal space. The hilum of the lung was dissected and the pulmonary artery freed and isolated. The mediastinal pleura was opened and the origin of the subclavian artery was dissected.

The graft was obliquely trimmed on the subclavian artery side. The length of graft was adjusted so that it lay straight along the mediastinum. The subclavian artery was clamped with a curved, noncrushing vascular clamp proximally and occluded with tape distally. An appropriately sized arteriotomy was done, and an anastomosis between the graft and the subclavian artery was performed with a running 7-0 prolene suture. With the clamp on the subclavian artery kept closed, the pulmonary artery was occluded proximally, with a clamp and distal snares snugged down around the branches. A transverse incision was performed in the upper face of the pulmonary artery, and an anastomosis was made with a running suture of 7-0 prolene. The chest was closed after a chest tube was placed on an underwater seal.

Four patients were neonates, ages 9-23 days. In this group, the MBTS was constructed during cardiopulmonary bypass (CPB) because the patients had pulmonary atresia and were at high risk for severe intraoperative arrhytmia and severe hypoxia during pulmonary artery clamping. In the remaining patients, the procedure was performed through a thoracotomy. In patients who underwent CPB, 3 mg/kg heparin was given before the initiation of CPB, and in the remaining patients, 2 mg/kg heparin was administered intravenously before the subclavian artery was clamped. In performing the anastomosis, we took special care to avoid grasping the BMVG with forceps. In 2 patients the BMVG was clamped for bleeding control, but the vascular clamp was not used in the remaining 11 patients. The shunt material was occluded with pressure of the fingers or with a bull-dog clamp. In all patients, heparin was fully neutralized after the procedures. None of the patients received anticoagulants or aspirin postoperatively.

Data Collection

Demographic data were collected on the group II patients and compared with the data for groups Ia and Ib. Graft patency was measured after surgery, before discharge, and at 1, 3, and 6 months during follow-up with echocardiography. Postoperative data, such as the occurrence of complications, were also collected.

Statistical Analysis

Statistical analysis was performed using the Pearson 2 test or the 2-sided Fisher exact test. Statistical significance of potential outcome variables was defined at the 95% confidence level ($P < .005$).

RESULTS

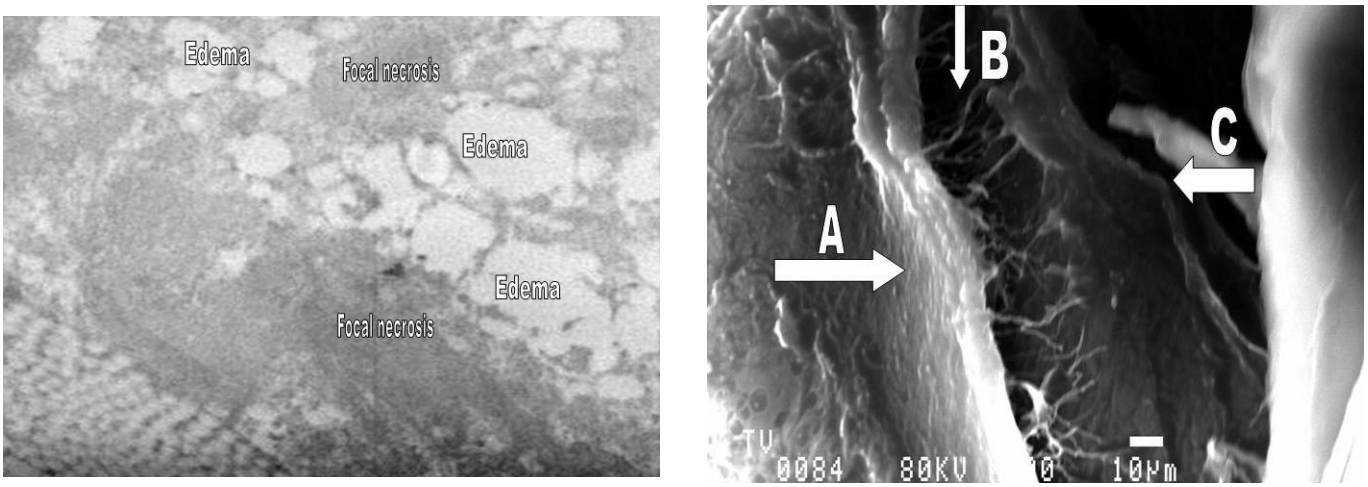
The mean age in group II was 3.7 ± 1.7 months. Demographic data revealed no statistically significant differences between the patients in group II and those in group Ia and group Ib (Table 1). Primary diagnosis of patients in group II is also shown in Table 1. Results of thrombophilic factors in group II were similar to those in group Ia (Table 2), showing no statistical difference. Therefore patients in group II were considered to be at risk for graft thrombosis in case of MBTS with a PTFE graft. Perioperative mean arterial oxygen saturation immediately increased to 78%-85% after the shunt procedure. There were no operative or postoperative deaths. A shunt murmur was present in all cases, and cyanosis was minimal at rest, with transcutaneous oxygen saturation varying between 75%-86%.

Three of 13 patients developed shunt failure in the early postoperative period. The general condition of these patients deteriorated suddenly on postoperative day 5 and 6. Echocardiography showed nearly occluded shunts. In the first case, the patient underwent a shunt revision 6 days after the initial operation. In the revision, we observed kinking of the BMVG, and in this patient the MBTS was reconstructed with an ePTFE after thrombectomy was performed. In the other 2 patients, clamping of the BMVG occurred. In one of these patients, the clamping was revised surgically by constructing a new MBTS with ePTFE. Histopathologic examination of the ring of the graft material revealed subadventitial necrosis and subintimal vacuolization (Figure). Antiaggregant therapy and anticoagulation was started in this patient. In the second patient with clamping of the BMVG, transcatheter balloon angioplasty and thrombolysis was successfully performed in the catheterization laboratory, with excellent results. Five days later, heparin was stopped and antiplatelet regimen continued. This patient was discharged with a regimen of antiplatelet and oral anticoagulant.

During surgery there was no bleeding from needle stitches and no signs of complications related to the shunt procedure, such as seroma, drainage, hematoma, or infection. Except for the 3 cases of shunt failure, all shunts were patent and functioning well after an avarage follow-up time of 10.5 months, despite no postoperative antiplatelet and anticoagulant regimen.

DISCUSSION

Although definitive repair of cyanotic congenital heart disease in the neonatal period is preferred, the application of MBTS continues to play an important role in the palliation of a variety of lesions. However, these shunts are at risk for occlusion related to intraluminal thrombosis, suture line stenosis, or



Scanning electron microscope images showing subadventitial necrosis, subintimal vacuolization, and severe edema between intercellular spaces due to vascular clamping. A. Three layers of the BMVG graft (A, adventitia; B, media; C, intima) separated after the use of vascular clamp. B. Histopathologic examination of the ring of the graft material revealed subadventitial necrosis and subintimal vacuolization.

intimal hyperplasia [Fermanis 1992; Tsai 1996; Gladman 1997; Al Jubair 1998; Motz 1999].

Despite much research, the "perfect" graft material has not been found. The classical subclavian-to–pulmonary artery shunt was later modified and PTFE grafts were introduced. Later on several different types of graft materials were used for MBTS construction. The use of the internal thoracic artery as a systemic-to–pulmonary artery shunt was first reported by Cobanoglu and coworkers in 1984. Tam et al [2001] published their results on the use of a saphenous homograft as a biologic conduit for the systemic arterial shunt in the Norwood procedure, and Leao and colleagues [1984] used an umbilical vein graft to perform the MBTS. Kalangos et al [2001] first described the use of BMVG for MBTS construction. Encouraging results were demonstrated in these studies, but each study has its own limitations. No previous investigation of the thrombophilic risk factors in candidates for MBTS has been reported, however.

Lower body weight, young age, small graft size, and pulmonary artery anatomy are accepted predictors of early and intermediate graft failure. In our series all patients showed similar demographic data, including body weight, and graft size was homogeneous in all groups. We performed our initial study to investigate whether graft failure may also be associated with thrombophilic risk factors such as high levels of factor II, factor V, factor VII, factor VIII, factor IX, factor XII, von Willebrand factor, and homocysteine; low levels of protein C, protein S, and antithrombin III; and the presence of factor V Leiden mutation, activated protein C resistance, and prothrombin G20210A mutation.

In this series, graft failure developed in 16.2% of 37 patients, a rate comparable to previously reported results, which vary between 7% and 20% [Sivakumar 2001]. Our study patients who developed graft failure demonstrated high levels of factor II, factor VII, factor VIII, and von Willebrand factor as well as low levels of protein C and protein S. To our knowledge, no previous reported study analyzed a broad spectrum of thrombophilic risk factors. Based on the results of statistical analyses, we developed parameters for identification of thrombophilic risk factors for graft failure and for patients with these risk factors we used BMVG for MBTS construction as described by Kalangos et al [2001], who initially reported the use of BMVG as a shunt material for the MBTS procedure without an antiplatelet regimen in neonates [2001]. However, our experience showed that the use of BMVG requires some special care, such as avoiding clamping. With experience we perfected the BMVG technique, avoiding the clamping and kinking, which occurred in 2 of our patients who required revision. Furthermore Kalangos et al [2001] showed that in both early and late postoperative periods graft patency was achieved despite the avoidance of anticoagulant and antiaggregant regimen. Although the use of synthetic graft materials has been reported by a number of authors, BMVG is not routinely used for the creation of MBTS, but BMVG is widely used to create arteriovenous fistulas in hemodialysis patients [Glickman 2004; Hatzibaloglu 2004]. Although there are several reports about the use of BMVGs in arteriovenous fistula creation, only one [Kalangos 2001] reports short and midterm results of BMVG in MBTS. To our knowledge, our study describes the largest series of BMVG-constructed MBTS and early and midterm findings in patients with CCHD with thrombophilic risk factors.

Persistant serum leakage through PTFE grafts causing perigraft seroma is a rare but devasting complication resulting in increased duration of tube drainage or the need for reinsertion of chest tubes, prolonged hospital stay, and multiple operations [Dogan 2005]. We did not observe seroma formation or graft infection after the use of BVMG. Additionally, we did not observe any sign of graft infection. The surgical technique is not difficult, but special care must be taken to avoid grasping the BVMG with forceps. In addition, clamping of the BVMG should be avoided because clamping damages the intimal layer

of the graft (O.F.D., unpublished data). If necessary the BVMG should be occluded with pressure of the fingers or a bull-dog vascular clamp, never with the standard vascular clamp. In our series shunt failure occurred in only 3 patients and was attributed to less surgical experience with this graft. One of these shunt failures was attributed to thrombosis due to kinking of the graft and the other 2 to crushing of the intimal layer of the BMVG. The other 10 patients showed an uneventful course during a mean follow-up period of 10.5 ± 0.5 months, despite no anticoagulant or antiplatelet regimen. These results were interpreted as encouraging.

In conclusion, preoperative assessment of thrombophilic risk factors is important in the prevention of thrombotic occlusion of MBTS with PTFE, and shunt thrombosis is possible in patients with positive thrombophilic risk factors even when antiplatelet therapy is administered. BMVG seems to be a feasible alternative for MBTS, despite some special considerations regarding surgical technique, such as the avoidance of clamp usage. BMVG does not require anticoagulation or antiplatelet regimen, which may be contraindicated in some cases. The absence of bleeding complications, seroma or hematoma formation, and infection are advantages of BMVG. A randomized trial comparing PTFE with properly handled BMVG in unselected patients with comparable medical management would help to determine the role of BMVG in the management of CCHD with concomitant thrombophilic risk factors.

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