The Contegra bovine jugular vein graft versus the Shelhigh pulmonic porcine graft for reconstruction of the right ventricular outflow tract: A comparative study

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Objectives: Reconstruction of the right ventricular outflow tract plays a major role in congenital cardiac surgery. With the advent of the Contegra bovine jugular vein graft and the Shelhigh pulmonic xenograft, hopes were high that the lack of availability of homografts would be overcome. The present study evaluated both grafts and investigated the influence of known risk factors for premature graft failure.

Methods: From December 1999 to September 2008, 84 consecutive patients (mean age, 12 ± 15 years) with a total of 100 implanted conduits (43 Contegra bovine jugular vein grafts and 57 Shelhigh pulmonic xenografts) were included in this study. Primary end points were reintervention, reoperation, and death.

Results: The rate of overall conduit replacement was 25% for the Shelhigh pulmonic xenograft versus 26% for the Contegra bovine jugular vein graft. The predominant mode of failure was conduit stenosis for both groups (23% for the Shelhigh pulmonic xenograft vs 19% for the Contegra bovine jugular vein graft), with a mean time to replacement of 18 ± 9 months for the Shelhigh pulmonic xenograft versus 42 ± 4 months for the Contegra bovine jugular vein graft ($P = .25$). Histopathological analysis revealed a similar chronic inflammatory reaction in both conduits, but it was significantly stronger in the Shelhigh pulmonic xenograft group. The Contegra bovine jugular vein graft showed frequently the formation of a stenotic membrane at the distal anastomosis site. Age of less than 1 year, body surface area, pulmonary stenosis, and conduit size of less than 14 mm could not be identified as risk factors for premature failure.

Conclusions: Both conduits fail predominantly because of stenosis and are subject to a chronic inflammatory reaction, although this was stronger in the Shelhigh pulmonic xenograft group. Mean time to replacement was 18 ± 9 months for the Shelhigh pulmonic graft group versus 42 ± 4 months for the Contegra bovine graft group ($P = .25$). Because there is a trend toward earlier failure in the Shelhigh pulmonic xenograft group, we currently prefer to implant the Contegra bovine jugular vein graft for right ventricular outflow tract reconstruction. (J Thorac Cardiovasc Surg 2011;141:654-61)

Reconstruction of the right ventricular outflow tract (RVOT) plays an important role in congenital cardiac surgery. The advances in correcting complex congenital cardiac malformations created an increasing demand for right ventricle (RV)–pulmonary artery (PA) conduits. Especially for small sizes, the availability of homografts is limited. With the advent of the Contegra bovine jugular vein graft (CBG; Medtronic, Inc, Minneapolis, Minn) and the second-generation Shelhigh pulmonic xenograft (SPG; NR-4000PA; Shelhigh, Inc, Millburn, NJ), it seemed that

this lack could be overcome. After initial promising results for both grafts,¹⁻³ reports regarding unexpected early failure in the CBG,⁴ as well as the SPG,⁵ dampened the optimism. Several studies were published reporting early and midterm results for either conduit and showed the failure of the grafts because of stenosis at the distal anastomosis or marked aneurysmal dilation with the CBG or excessive neointimal proliferation with the SPG. In our initial experience the CBG showed good hemodynamic performance, but after a mean follow-up of 18 months, 16% of the grafts had to be replaced.^{6,7} Immunogenic properties of the graft material leading to excessive intimal peel and perigraft scarring, as well as risk factors, such as small conduit size and the presence of pulmonary stenosis (PS), or technical aspects of implantation, were frequently discussed to be responsible for early conduit failure. However, until the present, the diversity of the findings of published studies could not clearly identify reasons for the observed differences in graft durability and mode of failure. Neither was it possible to demonstrate advantages of one type of conduit over the other. Thus far, there is no report of

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Abbreviations and Acronyms

CBG	= Contegra bovine jugular vein graft
CRP	= C-reactive protein
DORV	= double-outlet right ventricle
PA	= pulmonary artery
PS	= pulmonary stenosis
RV	= right ventricle
RVOT	= right ventricular outflow tract
SPG	= Shelhigh pulmonic xenograft
TGA	= transposition of the great arteries
VSD	= ventricular septal defect

simultaneous experience with both conduit types, and to the best of our knowledge, no randomized controlled trials have been conducted. The present study reports a single-center experience with the 2 xenograft RVOT conduits, the CBG and the second-generation SPG, for RVOT reconstruction from December 1999 to September 2008 in a constant surgical environment.

Up to now, young age of the patient (<1 year), small conduit size (<14 mm), and presence of PS are considered risk factors in determining graft durability. The present study investigates the influence of these characteristics on conduit durability.

MATERIALS AND METHODS

From December 1999 to September 2008, 84 consecutive patients (mean age, 12 ± 15 years) with a total of 100 implanted conduits (43 with the CBG and 57 with the SPG) were included in the present study. RVOT reconstruction became necessary because of various congenital cardiac defects, comprising both patients with primary procedures and those with reoperations. Choice of conduit was primarily based on availability and can be divided into 3 phases. With its introduction in 1999, we started primarily implanting the Contegra graft (phase 1) until reports of early failure and the advent of the second-generation Shelhigh graft. After a year of overlap (2003), we continued with the Shelhigh graft (phase 2) from 2004 until early 2007, when, after unexpected failure in several pediatric but also adult patients, we abandoned the use of all Shelhigh products. Since then, the CBG has been our preferred conduit (phase 3). During the study period, we implanted 15 homografts, mainly in patients with endocarditis or older patients undergoing RVOT replacement in whom either of the other grafts had failed more than once. Primary end points were reintervention, reoperation, and death. An RV-PA gradient of greater than 50 mm Hg was considered to be a significant conduit stenosis. Follow-up was performed by means of echocardiographic analysis or magnetic resonance imaging as appropriate at 0, 3, 6, and 12 months after surgical intervention and then once a year, depending on the findings. All other techniques of RVOT reconstruction (transcatheter patch, monocusp xenograft, and homograft) are excluded from this report.

Surgical Technique

Techniques for RVOT reconstruction remained constant during the study period. We only used non-ring-enforced CBGs, as well as second-generation SPGs with a bovine pericardial tube graft instead of a porcine PA as in the first generation. The conduits were treated according to the

specifications of the manufacturer. For the CBG, 3 sterile bowls containing 500 mL of physiological electrolyte solution were prepared for rinsing. The graft was taken out of the jar with atraumatic forceps, and residual storage solution was drained. After the graft was rinsed 3 times for 5 minutes in the 3 bowls containing the physiological electrolyte solution and left in the last bowl until needed for implantation. In contrast to the CBG, a rinsing procedure is not required by the handling instructions of the manufacturer for the SPG but could be performed, if wished, by rising it in 500 mL of saline solution for at least 2 minutes. Thus the SPGs were rinsed in 500 mL of saline solution for 2 to 3 minutes before implantation. Both conduits were always implanted with the valve as distal as possible. In case of redo surgical intervention, residual conduit material was completely removed. The "hood" of the proximal anastomosis was performed without additional prosthetic material, whereas bovine pericardial patches were used when augmentation of the PAs became necessary. The distal anastomosis was performed in an end-to-side fashion by using a continuous polypropylene suture if no stenosis of the PA was present. If the anastomosis includes the bifurcation itself or a stenosis is present, the PA is incised, and a more elliptical anastomosis is created to allow for a harmonious transition. Surgical intervention was performed by using all levels of extracorporeal support from deep hypothermic circulatory arrest to moderate hypothermia and beating heart surgery.

Data Collection

Data were collected in a prospective fashion according to European Cardiac Surgery Registry criteria. Furthermore, a special database for patients with RVOT conduits was initiated. The study was approved by the institutional review committee, and informed consent was obtained.

Statistical Analysis

Data analysis was performed by a statistician (BG) unaware of the clinical situation and outcome. In addition to descriptive statistics, data underwent a Kaplan-Meier survival analysis, with explanation caused by stenosis as an event, followed by a log rank test to compare the event risk for the 2 types of conduits. A Cox regression analysis to identify independent risk factors for graft failure, such as age, conduit size, and PA stenosis, was calculated. Analysis was performed with SPSS version 15.0 software (SPSS, Inc, Chicago, Ill).

RESULTS

Surgical intervention was performed in 84 patients, implanting 100 conduits because of tetralogy of Fallot ($n = 46$), pulmonary atresia ($n = 3$), isolated PS ($n = 4$), double-outlet right ventricle (DORV)/PS ($n = 3$), DORV/transposition of the great arteries (TGA; $n = 3$), TGA/ventricular septal defect (VSD)/PS ($n = 7$), truncus arteriosus communis ($n = 4$), pulmonary insufficiency ($n = 1$), and Ross procedures ($n = 13$). Overall follow-up was 100% complete, with an average time of 45.5 ± 29.4 months. Because of market introduction and availability, there was a significant difference in follow-up time ($P = .02$) for the 2 grafts, with an average of 57 ± 40 months in the CBG group and 37 ± 12 months in the SPG group. The mean age in the CBG group was 4.5 ± 5.5 years versus 18 ± 17.6 years in the SPG group ($P < .0001$). Comparison of both groups showed that children less than 1 year of age were more prevalent in the CBG group (33% [$n = 14$] vs 16% [$n = 9$]) than in the SPG group, although this did not reach statistical significance ($P = .06$). Mean body

FIGURE 1. Kaplan–Meier curve for freedom from explantation for Shelhigh pulmonic xenografts (gray line) and Contegra bovine jugular vein grafts (black line). Patients at risk are shown for both groups in corresponding numbers in brackets. The dashed line marks the performance of both conduits at 24 months.

surface area was $0.69 \pm 0.4 \text{ m}^2$ versus $1.22 \pm 0.6 \text{ m}^2$ ($P < .0001$), and mean conduit size was 16 mm in the CBG group versus 20 mm in the SPG group ($P < .0001$). The presence of PS was equally distributed between groups (84% vs 79%, $P = .61$).

The rate of reintervention was equal in both groups (2% [$n = 1$] in the SPG group vs 2% [$n = 1$] in the CBG group). Because reinterventions by means of balloon dilatation were not successful, these patients consecutively underwent reoperation.

The overall rate of replacement was 26% ($n = 11$) in the CBG group and 25% ($n = 14$) in the SPG group. Reoperation caused by stenosis became necessary in 19% ($n = 8$) in the CBG group and 23% ($n = 13$) of the SPG group ($P = .14$, Figure 1). The RV–PA maximal pressure gradient value before redo surgical intervention was $69 \pm 29 \text{ mm Hg}$ in the CBG group versus $76 \pm 28 \text{ mm Hg}$ in the SPG group ($P = .6$). Other reasons for conduit exchange included suspected endocarditis in 7% ($n = 3$) of the CBG group and 1.8% ($n = 1$) of the SPG group, respectively. Replacement because of stenosis within the first 2 years was performed in 9% ($n = 4$ of a total of 8 stenotic CBGs) of patients in the CBG group and in 18% ($n = 10$ of a total of 13 stenotic SPGs) of patients in the SPG group ($P = .38$). The mean time to replacement because of conduit stenosis was found to be 42 ± 35 months in the CBP group versus 18 ± 9 months in the SPG group ($P = .25$, calculated with a log rank test on the basis of the Kaplan–Meier survival model, thus taking into account the risk for explantation rather than

FIGURE 2. Scatter plot for time to explantation in the Shelhigh pulmonic xenograft and Contegra bovine jugular vein graft groups. A trend toward a shorter time span to explantation is demonstrated for the Shelhigh pulmonic xenograft group.

the time of explantation), and even though not significant, a trend toward earlier explantation was found for SPGs (Figure 2).

Regarding perioperative parameters, a significant difference for C-reactive protein (CRP) values was found between the 2 groups. Patients receiving a SPG showed a significantly higher mean increase ($100 \pm 79 \text{ mg/L}$, $P = .001$), as well as a higher maximum level ($114 \pm 88 \text{ mg/L}$, $P < .0001$), of CRP compared with that seen in patients receiving a CBG (mean increase, $46 \pm 49 \text{ mg/L}$; maximal level, $48 \pm 49 \text{ mg/L}$). Patients with a confirmed bacterial or viral infection were excluded. In the SPG group 75% of patients received aspirin immediately postoperatively, whereas this was only the case in 26% of patients in the CBG group; oral anticoagulation was initiated in 9% of the SPG group and 5% of the CBG group.

Explanted conduits were sent to pathology for histological and immunohistochemical analysis, which revealed a chronic inflammation with foreign body reaction and lymphocyte infiltration for both conduits (Figure 3). The SPGs showed a severely thickened and fibrotic conduit wall, which was more pronounced than in the CBGs. In both conduits the valve leaflets were mostly found to be intact, pliable, and without infiltration. In contrast to the SPGs, in which the formation of a thickened and fibrotic conduit wall narrowed the internal lumen of the graft over its full length, the CBGs demonstrated deposition of a fibrous, paucicellular tissue and fibrin deposition on its luminal aspect, although with a narrowing of the distal lumen of the graft by the formation of a fibrotic membrane. For both grafts,

FIGURE 3. Histopathology of explanted Shelhigh pulmonic xenograft and Contegra bovine jugular vein graft conduits. A, Explanted longitudinally opened Shelhigh pulmonic xenograft showing a thickened and fibrotic conduit wall with thin and pliable valve leaflets. B, Hematoxylin and eosin staining of a Shelhigh pulmonic xenograft and overview of the graft material. The partially destroyed graft material (SG) is surrounded by granulation tissue, with accumulation of macrophages and lymphocytes and numerous foreign body multinuclear giant cells. The luminal aspect (#) reveals substantial fibrosis and focally paucicellular scar tissue. The adventitial aspect (*) shows formation of a wide neoadventitia penetrated by strong inflammatory infiltrate. The black arrow denotes suture material in situ. C, Hematoxylin and eosin staining of a Shelhigh pulmonic xenograft revealing a partially destroyed graft material. Florid granulation tissue takes up much of the image (*), bordered in part by paucicellular scar tissue. The predominantly macrophage- and lymphocyte-rich inflammatory infiltrate also reveals numerous foreign body multinucleate giant cells (black arrows). These giant cells are in part found surrounding suture material but are also located along the outer aspect of the graft boundaries, as well as in the vicinity of largely degraded collagenous graft fibers. Grouped microcalcifications (white arrows) are occasionally located within the graft wall. D, Masson trichrome staining of a Shelhigh pulmonic xenograft with overview of the graft from the inner luminal aspect with the attached valve leaflet (left) to the adventitial aspect (right). The valve leaflet is essentially intact and delicate, without significant inflammatory infiltrate or fibrosis. The luminal aspect is characterized by a fibrous paucicellular tissue and fibrin deposition delineated by a mixed inflammatory infiltrate. E, An explanted longitudinally opened Contegra bovine jugular vein graft revealing a fibrotic membrane formation at the site of the distal anastomosis. The Contegra bovine jugular vein graft leaflets appear intact, thin, and pliable. F, Hematoxylin and eosin staining of a Contegra bovine jugular vein graft showing a continuous fibrin deposition on the intimal aspect (upper side of the specimen). The whole graft

histology and immunohistology showed partially destructed graft material with degraded collagen fibers, which was surrounded by florid granulation and scar tissue with accumulation of macrophages, lymphocytes, and numerous foreign body multinuclear giant cells. The luminal aspect reveals substantial fibrosis and focally paucicellular scar tissue. The adventitial aspect shows formation of a wide neoadventitia penetrated by strong inflammatory infiltrate. Focal microcalcifications were observed within both conduit walls.

Overall hospital and long-term mortality was 8% ($n = 3$) in the CBG group versus 4% ($n = 2$) in the SPG group. Of the 3 patients in the CBG group, one child died of acute right heart failure during anesthesia induction before reoperation for conduit exchange. The second child died after correction of DORV with complete pulmonary atresia and VSD after unsuccessful weaning from postcardiotomy extracorporeal membrane oxygenation support. The third child underwent corrective surgical intervention for complex TGA with inlet VSD and hypoplastic aortic valve. The child experienced severe respiratory failure and died on postoperative day 2 on extracorporeal membrane oxygenation support. In the SPG group 1 child died of unclear reasons, most probably arrhythmia, several months postoperatively after correction of aortic stenosis by means of a Ross procedure. Autopsy was performed and showed an unremarkable situs. The second child in the SPG group died of postoperative circulatory failure after a complex fourth reoperation with conduit exchange for correction of a DORV.

Regression Analysis

A Cox regression analysis was performed regarding the expected influence factors of age, presence of PS, and conduit size for premature conduit failure. Conduit type was also included in the analysis. This did not lead to a prediction model of the hazard ratio for conduit failure. Surprisingly, of all possible influence factors, conduit type was the closest to reaching significance ($P = .06$), whereas the other factors were far off: age less than 1 year ($P = .48$), body surface area ($P = .96$), presence of PS ($P = .51$), and conduit size less than 14 mm ($P = .24$). Given the dif-

ferent odds ratios of conduit type, one could see a trend toward better performance in the CBG group by reduction of the probability of explantation by 60%. However, it has to be taken into consideration that this is based on an overall nonsignificant prediction model.

Limitations

Because the conduits did not appear simultaneously on the European market, this results in an unequal follow-up. Additionally, selection of the conduits was biased by the availability of the conduit and the choice of the surgeon during phase 2 of the study.

DISCUSSION

Homografts present the benchmark for RVOT conduit performance, with an approximate 10-year freedom from reoperation of 60% to 90%.^{8,9} The most common mode of premature failure for homografts is early calcification and valve insufficiency, especially in patients with increased PA pressure. Freedom from reoperation varies according to the patient population. Age and conduit size have been determined as independent risk factors for freedom from reoperation. Immunologic factors, such as blood group incompatibility, are also discussed to influence homograft durability because several reports have shown better results when using matched homografts.^{10,11}

Comparing conduit performance is difficult. A definitive statement about conduit performance would require a patient population with the same defects in the same age group and equally distributed primary procedures and reoperations. A conduit used to replace the pulmonary valve in a Ross procedure will perform differently from an RVOT conduit in the setting of a hypoplastic PA with severe pulmonary hypertension. Furthermore, it can be difficult to distinguish between real premature conduit failure and failure caused by normal somatic outgrowth. Especially in small conduit sizes (10 or 12 mm), a very large patient cohort would be required to demonstrate a significant difference and at the same time eliminate the bias of somatic outgrowth.

is penetrated by a strong inflammatory infiltrate with macrophage and lymphocyte accumulation and giant cell reaction. Infiltration is observed in all layers but is most prominent within the adventitia, as well as on the internal luminal aspect of the graft. The media reveal tears and focal microcalcifications. Collagen fibers are partially destructed. G, Masson trichrome staining, with an overview of a transverse section through the Contegra bovine jugular vein graft at the site of anastomosis to the pulmonary artery. The inner lumen (*) is substantially narrowed by a fibrous membrane (**). The graft itself is covered on the inner aspect with a thin pseudointima largely devoid of an endothelial lining. The adventitial aspect (***) reveals focal thickening and fibrosis. Circumscribed areas of fibrin deposits (') between the inner fibrous ring and outer aspects of the graft wall are shown. Arrows denote the points of anastomosis between the pulmonary artery and Contegra graft. The rectangle denotes the area shown enlarged in panel H. H, Enlarged image of the point of anastomosis (white arrow) between the pulmonary artery (*) and Contegra bovine jugular vein graft (#). Black arrows point to artificial lumina representing channels from suture material removed in the process of sample preparation. The arrowhead reveals an area of palisading foreign body multinucleate giant cells bordering the Contegra bovine jugular vein graft material. The elastic lamellae of the pulmonary artery are partially loosened, and fibroblast infiltration and collagenous scar tissue are apparent in this area.

TABLE 1. Literature overview of CBG and SPG studies

Author	Year of publication	SPG,1; CBG, 2	No. of patients	Conduits (n)	Mean age (y)	Ross procedure (%)	Redo operations (%)	Mean follow-up	Explantation (%)	Reintervention (%)
Marianeschi et al ¹²	2001	1	25	25	20.2	68	32	30	8	0
Ishizaka et al ⁵	2003	1	24	25	2.8	0	NA	23	48	8
Schreiber et al ¹³	2006	1	34	34	0.6	0	27	12	44	0
Kim et al ¹⁴	2007	1	73	81	6.8	4	NA	11	12.3	0
Carrel et al ⁶	2002	2	21	22		0			4.5	9.1
Corno et al ²²	2002	2	26	26	13.5	42	NA	15	0	0
Bove et al ²¹	2002	2	41	41	1.9	12	20	NA	0	0
Breymann et al ¹⁵	2004	2	104	108	4.3	1	69	25	8	NA
Corno et al ¹	2004	2	67	67	16.1	40	58*	26	1.5	7.5
Meyns et al ²⁰	2004	2	57	58	9	17	53	23	12	29
Tiete et al ¹⁷	2004	2	29	29	3.4	0	41	10	3.4	6.9
Goeber et al ⁷	2005	2	36	38	2.1	0	NA	18	16	0
Brown et al ¹⁶	2006	2	62	62	7.3	6	63	26	1.6	11.3
Rastan et al ²³	2006	2	78	78	12.9	NA	72	31	12.8	24.4
Shebani et al ¹⁹	2006	2	62	64	1.2	0	19.4	14	6.3	9.4
Sierra et al ²⁴	2007	2	50	50	4.9	0	24	28	4	0
Sekarski et al ¹⁸	2007	2	133	133	2.6	15	NA	32	9	9

CBG, Congrega bovine jugular vein graft; NA, not applicable; SPG, Shelhigh pulmonic xenograft. *Including interventional procedures.

As already mentioned, there is no study comparing CBGs and SPGs, let alone a randomized controlled trial. Four bigger studies have thus far provided original data on the follow-up of the SPG (Table 1).^{1,5,6,7,12-24} Marianeschi and colleagues¹² published the first results on SPGs, mainly based on patients undergoing a Ross procedure with a median age of 20.2 years. The SPGs performed well in this patient population and promised to be an alternative to homografts. In 2003, Ishizaka and associates⁵ and in 2006 Schreiber and coworkers¹³ published their results in a pediatric population. Ishizaka and associates⁵ reported 25 patients with a mean age of 2.8 ± 3.9 years. After a mean follow-up of 23 ± 5 months, 48% of conduits had to be replaced, and the group abandoned the use of the SPG. Schreiber and coworkers¹³ operated on 34 patients with a mean age of 7 months and had to replace 15 conduits after medium follow-up of 1 year. Kim and associates¹⁴ reported a freedom from reoperation of only 33.3% within the first 12 months in small conduits but an overall rate of freedom from reoperation of 87% after 24 months.

In our present study, with a wide span of age and a broad spectrum of defects, the SPG performs better than in the infant population described by Schreiber and coworkers.¹³ The graft had to be replaced because of stenosis in 18% of the patients after 2 years and in 25% after a follow-up of 37 ± 12 months. Nevertheless, the mean time to replacement in the SPG group was short at only 18 ± 9 months. In contrast to the study by Kim and associates,¹⁴ conduit size was not an independent risk factor for reoperation.

The literature regarding the CBG is much more diverse (Table 1). The initial results after the CBG was introduced to the European market in 1998 within the setting of clinical

studies were very encouraging. Breymann and colleagues¹⁵ reported 71 patients with a low median age of 1.2 years. During a mean 27-month follow-up, no conduit failure was observed. All reoperations in this series were reported to be not conduit related. Brown and coworkers¹⁶ published results on 62 patients, including 39 with a failed pulmonary homograft. Mean time to reoperation was 11 ± 8 months, with 1 conduit replacement and 7 patients undergoing percutaneous intervention. In parallel, reports of conduit failure because of aneurysmal dilatation, thrombosis, and early stenosis were published.^{4,7,17,25,26} In contrast to the good to excellent results (ie, zero conduit failure, as reported by Breymann and colleagues¹⁵), the mean time to replacement of CBG conduits in our population was 42 ± 35 months during an average follow-up of 57 ± 40 months among our CBG patient group. The mean age of the patients was 4.5 ± 5.5 years. The difference among the results for the durability of the CBG, as observed by us and others, is still a matter of ongoing discussion. Consistent with contemporary reports, the predominant mode of failure was progressive stenosis of the graft with frequent formation of a stenotic membrane at the distal anastomosis sometimes associated with aneurysmal dilatation. We did not observe any valve insufficiency leading to replacement. In a large series of 133 pediatric patients with a median age of 31 months, Sekarski and coworkers¹⁸ had to explant 13 conduits, 4 because of problems with the distal anastomosis, 3 because of endocarditis, 1 because of thrombosis, and 5 during reoperation for distal PA stenosis reported as being unrelated to the graft. Several studies reported early failure and aneurysmal dilatations of the CBGs to be associated with increased RV-PA pressures.^{19,26} Other than 2

patients who showed aneurysmatic graft dilatation caused by very severe stenosis of the distal anastomosis, this study could not determine PS as an independent risk factor for early graft failure.

Several explanations have been given for the repeatedly observed mode of failure of the CBGs caused by the formation of the fibrotic membrane at the distal anastomotic site. A contributing factor might be the proper rinsing of the Contegra graft. It has been suggested that trimming the distal part of the graft only after rinsing could lead to residual glutaraldehyde in the distal suture line and might promote stenosis.²⁰ An additional technical aspect leading to fibrotic deposition and membrane formation presents the incorporation of adventitial tissue into the internal surface of the conduit-PA anastomosis. We are not aware of implanting the graft in such a fashion, and the distal anastomoses were performed by using a standard end-to-side technique with a continuous Prolene (Ethicon, Inc, Somerville, NJ) suture line.

Given our histopathological findings, immunologic mechanisms appear to be more likely to be responsible for the early failure of CBG and SPG conduits. Both types of xenografts show a strong chronic inflammation, with foreign body reaction and lymphocytic infiltration. In contrast to the CBG, SBGs demonstrate a thickened and more fibrotic conduit wall that involves the whole graft, whereas the stenosis was predominantly located at the distal anastomosis in the CBGs. Such rather strong immunologic reactions are not reported for explanted homografts, even blood group-incompatible homograft implants.

Our observations are supported by other reports.^{20,27} Wojtalik and associates²⁸ demonstrated a B-cell increase of up to 150% of the normal value with T-lymphocyte activation and the presence of CD69⁺ and CD71⁺ cells after implantation of a CBG at 3 to 6 months postoperatively. The difference in the intensity of the immunologic reaction, with a macroscopically stronger fibrosis and thickening of the SPG throughout the whole conduit and a higher level of lymphocytic infiltration in all layers of the SPG compared with that seen in CBGs, correlates well with the observed higher frequency of postoperative fever and maximum and mean levels of CRP in the SPG group. Given these findings and reports of adverse events associated with other Shelhigh products, our group has stopped implanting Shelhigh-manufactured grafts.²⁹

Although the influence on graft durability is unclear, aspirin is frequently given postoperatively to improve graft durability. Most authors recommend aspirin for at least 3 months (3, 5, or 10 mg kg⁻¹ d⁻¹),¹⁵ but there are no studies regarding the direct influence on graft survival. In our study aspirin could not be determined as an independent factor to reduce the incidence of stenosis, but this might be due to the initially inconsistent regimen of postoperative aspirin ther-

apy in the absence of evidence and guidelines and to a certain extent due to the concerns of our cardiologists regarding Reye syndrome. Currently, all patients receive aspirin postoperatively at a dosage of 10 mg kg⁻¹ d⁻¹.

SUMMARY AND CONCLUSIONS

In the present study both xenograft conduits fail predominantly because of stenosis (23% for SPGs vs 19% for CBGs), with a mean time to replacement of 18 ± 9 months for the SPG versus 42 ± 4 months for the CBG ($P = .25$). The SPG shows a trend toward earlier explantation, with almost three fourths of the SPGs requiring replacement during the first 2 years. Cox regression analysis revealed the reduction of explantation probability by 60% by CBGs compared with SPGs and did not identify age of less than 1 year, body surface area, PS, and conduit size of less than 14 mm as risk factors for premature failure.

Histologic analysis demonstrated the formation of a thick fibrotic wall throughout the whole conduit in SPGs, whereas CBGs are frequently found to fail because of the formation of a stenotic membrane around the distal anastomotic site. A similar chronic inflammatory reaction was observed in both conduits after implantation; however, it appears that there is a stronger reaction in the SPG. Thus immunologic factors appear to be responsible for graft failure rather than technical aspects or patients' characteristics.

Given these findings, our current strategy is to implant pulmonary homografts in adult patients and to implant CBGs for the reconstruction of small-sized RVOTs in children when homografts are not available.

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