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Stenting the Arterial Duct in Neonates and Infants With Congenital Heart Disease and Duct-Dependent Pulmonary Blood Flow: A Multicenter Experience of an Evolving Therapy Over 18 Years

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Objectives: The primary aim of this multi-institutional study was to describe our 18-year experience of ductal stenting (DS) in infants with a duct-dependent pulmonary circulation. The secondary aim sought to identify a subgroup of patients who may benefit the most using this evolving technique. Background: No study has examined the extraordinary evolution of this promising therapy over the last two decades. Methods: Between 1991 and 2009, 65 neonates and infants (39 male, 60%) underwent cardiac catheterization for DS in 3 participating centres. Patients were divided according to whether DS was attempted between 1991–2000 (Group 1, $n = 20$) or between 2001–2009 (Group 2, $n = 45$). Results: DS was successful in 52/65 (80%) patients. DS outcome was associated with ductal morphology and cardiac diagnosis. DS failed more often in patients with univentricular physiology and tortuous duct morphology ($p < 0.001$). Most patients undergoing DS in Group 2 had pulmonary atresia with intact ventricular septum (PAIVS) ($p < 0.001$). DS was successful in 94% of these patients. Groups differed significantly in diameter and length of first implanted stent ($p < 0.001$), implanting additional stent ($p < 0.001$), and occurrence of complications ($p = 0.033$). Freedom from re-intervention for the 52 patients was 92.3%. No procedure-related mortality occurred. Conclusions: The technical aspects and clinical application of percutaneous DS has changed in the last two decades. DS has become a practical and safe therapy in a subgroup of neonates with ductal-dependent pulmonary blood flow.

Key words: arterial duct; stenting; congenital heart disease; tortuous duct; cardiac catheterization; intervention

INTRODUCTION

Neonates and infants with duct-dependent pulmonary blood flow are traditionally treated with a surgical systemic-to-pulmonary shunt [1,2]. Maintaining duct patency by stent implantation during an interventional cardiac catheterization procedure was first described in the early 1990s [3,4]. Since its first application, ductal stenting (DS) has been considered to be an attractive alternative to surgery in a subgroup of critically ill neonates and infants with congenital heart disease [4–9]. However, due to concerns of ductal patency after stenting and a relatively high complication rate after DS in the early days, its role as a reliable and safe alternative to surgery remains to be established [10–12].

With recent advances in stent, wire and balloon technology, DS has made an extraordinary evolution during the last two decades, with reported success rates of 80–100% in experienced hands [4–14]. Nevertheless, most reports have limited numbers of patients and

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Conflict of interest: Nothing to report.

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describe single centre experiences. Accordingly, the primary aim of this study was to describe our 18-year multicentre experience with neonates and infants undergoing DS for duct-dependent pulmonary circulation, focusing on the evolution of this procedure during this time interval. The secondary aim was to compare the demographics, anatomic and technical characteristics of DS to identify a subgroup of patients who may benefit the most using this evolving technique.

METHODS

Study Population

The records of all neonates and infants with duct-dependent pulmonary blood flow, undergoing cardiac catheterization for stent placement in the arterial duct at the (1) Evelina Children's Hospital, Guy's and St. Thomas' Hospital London, United Kingdom, (2) Cairo University Children Hospital, Cairo, Egypt, and (3) Heart Center, University Hospital of Cologne, Germany, between 1991 and 2009 were reviewed. Data were collected from first admission until last available follow-up. Medical records were searched for age at procedure, weight, cardiac diagnosis, procedural data including ductal anatomy, complications, type of stent used, reinterventions needed, outcome, and concomitant procedures, such as radiofrequency (RF)-assisted valvotomy and balloon dilation. Ductal anatomy was defined as (1) tubular or tortuous and (2) horizontal (arising from the descending aorta) or vertical (proximal aortic arch). Cardiac diagnoses were further described as either biventricular or univentricular physiology depending on proposed surgical therapy. Patients were then classified into two groups based on whether DS was attempted between 1991 and 2000 (group 1) or 2001–2009 (group 2). Participating centers contributed at least 15 patients each. However, patients were not equally distributed across the two groups, because not all centers started with DS in the early 90s.

The primary indications for DS included (1) a high surgical risk, as defined by the individual participating centers based on the availability of appropriate surgical facilities; (2) ductal morphology on echocardiography; in general a straight tubular duct was considered ideal for DS; (3) the duration for which ductal patency was desired, and especially if this was expected to exceed 2 weeks, (4) interventionalists' preference, and (5) availability of cardiac surgery.

In the early 90s, DS was primarily attempted in patients at high surgical risk. The indication for DS was then extended to patients with other indications enumerated above. In general, the judgment remained subjective, and was based on experience, learning curve, and the interventionalists' preference. The primary exclusion criterion for DS was complex ductal anatomy (tortuous ducts) as evaluated by echocardiography and in some patients subsequently confirmed by angiography. Especially later in the experience, this led to preference for surgery in centers where surgery was readily available, although DS was still attempted if the availability of cardiac surgery was limited.

Cardiac Catheterization and Interventional Procedures

All procedures were performed under general anaesthesia. Prostaglandin E infusion was discontinued in most patients 4–6 hr before stent implantation. In general, primary vascular access was obtained using the femoral or axillary artery. A 4 or 5F arterial sheath, for femoral access, and a 4F arterial sheath for axillary access, was placed in the aorta to delineate ductal size, length, and morphology using multiple angiographic projections. After optimal imaging of the arterial duct, it was decided if the duct could be accessed using the primary vascular access. When not, vascular access was created using an alternative route in selected patients (Fig. 1).

Next, a 0.014 inch coronary guidewire was passed through the duct and carefully placed in the left or right branch pulmonary arteries. In patients with PAIVS who had undergone radiofrequency assisted pulmonary valvotomy, the guide wire was placed across the duct into the descending aorta from the main pulmonary artery and the stent advanced from the femoral venous sheath. The length of the stent was chosen depending on the size and anatomy of the duct (tubular, tortuous), and the availability of stent lengths at that time. The diameter of the stent was chosen depending on: (1) the weight of the patient (the stent was inflated to a diameter of between 3 mm and 3.5 mm in patients weighing less than 3 kg; to between 4 and 4.5 mm diameter in patients weighing between 3 and 4 kg, and $>$4.5 mm in patients weighing 5 kg or more), and (2) the interventionalists' preference (in the earlier time-period, there was a tendency to aim for larger ductal diameters). After stenting, repeat angiography was used to evaluate the position of the stent, to exclude stent related pulmonary artery or aortic stenosis, and to reveal if the duct was completely covered. Prophylactic antibiotic therapy was given to all patients. Anticoagulation, using intravenous heparin, was changed to acetylsalicylic acid (3–5 mg/kg/day) for as long as stent patency was required. The minimal duration of heparin therapy was 24 hr.

The technique of catheter RF-ablation of the atretic pulmonary valve in PAIVS has been previously described elsewhere [4,21,23,25].

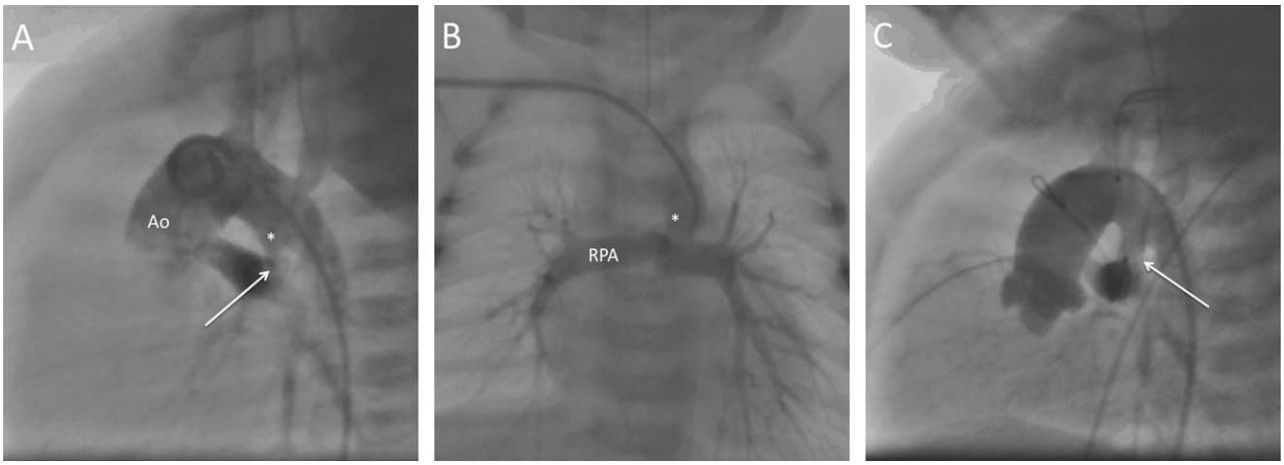

Fig. 1. Aortic angiogram demonstrating a straight vertical arterial duct (*) arising from the inner curvature of the aortic arch. The pulmonary end of the arterial duct is also shown (arrow) (A,B). Subsequently, the right axillary artery was accessed for ductal stenting. Lateral view showing the final stent-position in the arterial duct (arrow) (C). Ao, aorta; RPA, right pulmonary artery.

Statistical Analysis

Continuous variables were summarized as mean (SD) or median (range) as appropriate, depending on normality of distribution. Categorical variables are represented by frequencies and percentages. χ^2 and Fisher's exact tests were used for comparison of categorical variables. Continuous variables were compared using the Student's *t*-test or Mann-Whitney *U* test, when appropriate. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 19.0 for Macintosh.

RESULTS

Patient Characteristics

Median weight and age for the 65 patients undergoing cardiac catheterization to attempt DS were 3.2 kg (range 2.4–6.0 kg) and 9 days (range 2–249 days), respectively. Cardiac diagnoses for the whole group of patients included: pulmonary atresia with intact ventricular septum (PAIVS) $n = 33$ (50.8%), critical pulmonary stenosis (cPS) $n = 10$ (15.4%), pulmonary atresia with ventricular septum defect (PAVSD) $n = 4$ (6.2%), tetralogy of fallot (TOF) $n = 3$ (4.6%), of which 1 patient had duct-dependent left pulmonary artery blood flow (Fig. 2), atrioventricular septal defect (AVSD) with PS or PA $n = 4$ (6.2%), double inlet left ventricle (DILV) with PS or PA $n = 3$ (4.6%), tricuspid atresia (TA) $n = 3$ (4.6%), other types of univentricular hearts (UVH*) $n = 4$ (6.2%), double outlet right ventricle (DORV) with cPS $n = 1$ (1.5%). In total, 52 patients (80.0%) had biventricular and 13 patients (20.0%) had univentricular physiology. Patient characteristics according to whether they underwent DS during the "early days" of this evolving technique (group 1) or more recently (group 2) are summarized in Table I.

Interventional Procedure

DS was successful in 52/65 patients (80%). When comparing the subgroups, the difference in successful application of DS between both time periods was not significant (Group 1: success $n = 15/20$ (75%) vs. Group 2: success $n = 37/45$ (82%); $P = 0.502$). The transcutaneous O2 saturation increased in successfully stented patients from $83.1 \pm 5.7\%$ to $91.1 \pm 4.8\%$ ($P < 0.001$). Vascular access was obtained using the femoral approach in most patients (57/65 (87.7%), and in eight patients (Group 1: $n = 5$; Group 2: $n = 3$) using the axillary artery (12.3%). Clinical and hemodynamic characteristics of patients in which DS failed are shown in Table II. Stenting failed more often in patients with UVH and tortuous duct morphology ($P < 0.001$).

Concomitant Procedures

The concomitant procedures performed in our study were balloon dilation of the pulmonary valve in cPS, and RF-catheter perforation of the pulmonary valve and subsequent balloon dilation in patients with PAIVS (Fig. 3). This procedure was performed in 23/33 (69.7%) patients with PAIVS before DS was attempted. The remaining 10 patients with PAIVS did not undergo RF-assisted valvotomy due to lack of appropriate

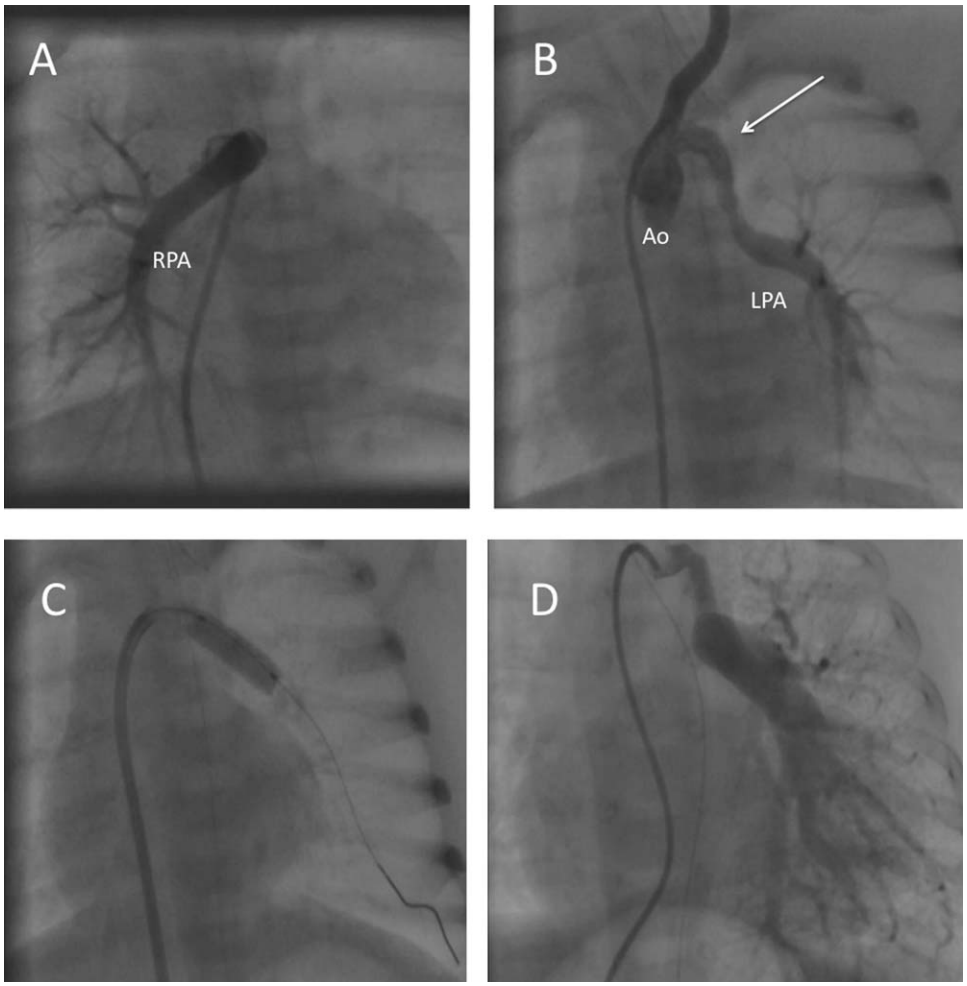

Fig. 2. Anteroposterior view after contrast injection in the pulmonary arterial trunk showing discontinuous pulmonary arteries (A). Aortic angiogram demonstrating the morphology of the arterial duct in the same patient. The left pulmonary artery was perfused by a long and curved, tubular arterial duct (arrow) (B). Final stent position after deployment (C). Selective angiogram demonstrating full-length coverage of the patent arterial duct (D). Ao, aorta; LPA, left pulmonary artery; RPA, right pulmonary artery.

equipment, facilities or expertise for this procedure. They are awaiting cardiac surgery.

Ductal Anatomy and Its Relation to Stenting Outcome

Ductal morphology was tubular in most patients ($n = 44$, 67.7%) and tortuous in 21/65 patients (32.3%). Duct morphology depended on type of congenital heart disease. All patients with cPS had horizontal tubular ducts. In the contrary, all patients with PAVSD had a tortuous duct. Moreover, a tortuous ductal course was demonstrated more often in patients with UVH (UVH: 11/13 patients (84.6%); biventricular: 10/52 patients (19.2%), $P < 0.001$), in which DS was more difficult ($P < 0.001$, Table II). When comparing subgroups, tortuous duct morphology was seen more commonly in the early days of DS (Group 1: 9/20 patients (45.0%); Group 2: 12/45 patients (26.7%), $P < 0.001$).

A detailed description of ductal morphology was available for 31 patients (Group 1: $n = 0$; Group 2: $n = 31$). A vertical duct was demonstrated by angiography in 8/31 patients (25.8%). The course of a vertical duct was tubular in 4/8 patients, and tortuous with multiple sharp curves in 4/8 patients. Stent implantation in a vertical duct with tortuous appearance was technically impossible in all cases (UVH $n = 2$, PAVSD $n = 2$). In 1 patient with PAIVS, a vertical tubular-shaped duct was seen arising from the left subclavian artery. This duct was successfully stented using the retrograde transarterial method. A horizontal type of arterial duct was observed in the remaining 23 patients (tubular course in 21 patients, tortuous in 2

TABLE I. Clinical Characteristics of 65 Infants Undergoing Ductal Stenting Between 1991 and 2009

	Total ($n = 65$)	Group 1 1991–2000 ($n = 20$)	Group 2 2001–2009 ($n = 45$)	P value
Age (days)				0.588
Mean ± SD	20.9 ± 36.0	24.5 ± 54.0	19.3 ± 24.7	
Median (range)	10 (2–249)	10 (2–249)	9 (2–120)	
Weight (g)	3256 ± 532	3193 ± 396	3285 ± 585	0.527
Male (n)	39	15	24	0.100
Physiology				0.007
Biventricular	52	12	40	
Single	13	8	5	
Diagnosis				
PA-IVS	33	6	27	<0.001
cPS	10	3	7	
PA-VSD	4	1	3	
DORV-cPS	1	0	1	
TOF	3	1	2	
AVSD-PA/PS	4	2	2	
Tricuspid atresia	3	1	2	
DILV-PA/PS	3	3	0	
UVH*	4	3	1	
Ductal anatomy				0.145
Tortuous	21	9	12	
Tubular	44	11	33	
Vertical		n.r.	8	
Horizontal		n.r.	23	
Successful stenting	52	15	37	0.502

AVSD, atrioventricular septal defect; cPS, critical pulmonary stenosis; DILV, double inlet left ventricle; PA, pulmonary atresia; PS, pulmonary stenosis; PAIVS, pulmonary atresia with intact ventricular septum; PAVSD, pulmonary atresia with ventricular septum defect; TA, tricuspid atresia; TOF, tetralogy of fallot; UVH*, other types of univentricular physiology.

patients). DS was feasible in all horizontal tubular ducts.

Need for a Second and Third Ductal Stent

Seventy-three stents were implanted in 52 patients. A total of 16/52 patients (30.7%) required more than one stent to cover the duct completely. The need for implanting more than one stent in the arterial duct differed significantly between both study groups (8/15 patients (53.3%, Group 1) vs. 8/37 patients (21.6%, Group 2), $P < 0.001$). Additional stents were implanted during the same procedure in all patients. A second stent was needed in 11/52 patients (21.1%), and a third in 5/52 patients (9.6%), respectively. Although there was a trend towards implanting more stents in patients with UVH and tortuous ducts, this difference did not reach statistical significance ($P = 0.118$).

TABLE II. Clinical Characteristics of 13 Infants in Which Ductal Stenting Procedure Failed

	Success ($n = 52$)	Failed procedure ($n = 13$)	P value
Age (days)	18.0 ± 35.5	32.5 ± 36.9	0.197
Weight (g)	3252 ± 572	3272 ± 350	0.906
Male (n)	15	8	0.899
Physiology			0.001
Biventricular	46	6	
Single	6	7	
Diagnosis			
PA-IVS	31	2	0.004
cPS	10	0	
PA-VSD	1	3	
DORV-cPS	1	0	
TOF	3	0	
AVSD-PA/PS	2	2	
Tricuspid atresia	1	2	
DILV-PA/PS	1	2	
UVH*	2	2	
Ductal anatomy			0.0001
Tortuous	10	11	
Tubular	42	2	

Abbreviations as in Table I.

Stent Size and Type

The diameter and length of the first implanted stent differed significantly between both groups (diameter of stent, Group 1: 4.7 ± 0.6 mm (range 4.0–6.0 mm), Group 2: 3.8 ± 0.4 mm (range 3.0–5.0 mm), $P < 0.0001$; stent length, Group 1: 13.6 ± 2.1 mm, Group 2: 17.2 ± 4.6 mm, $P < 0.0001$, respectively). Moreover, there was a significant difference in stent diameter and length between infants with tortuous compared to those with tubular duct morphology (diameter of stent, tortuous duct: 4.6 ± 0.7 mm; tubular duct: 3.9 ± 0.5 mm, $P < 0.005$; stent length, tortuous duct: 14.4 ± 3.8 mm; tubular duct: 16.6 ± 4.4 mm, $P < 0.005$).

The type of implanted stent differed between both eras. Tower stents ($n = 20$, diameter 4–6 mm, length 12–16 mm, in $n = 11$ patients) and Corinthian stents ($n = 8$, diameter 4–5 mm, length 10–16 mm, in $n = 4$ patients) were mainly used in Group 1. The Liberte stent ($n = 39$, diameter 3–4.5 mm, length 8–28 mm, in $n = 30$ patients), Corinthian stent ($n = 7$, diameter 4–5 mm, length 12–15 mm, in $n = 4$ patients), and Multilink Zeta stent ($n = 2$, diameter 3 mm, length 18–23 mm, in 2 patients) were used primarily in group 2.

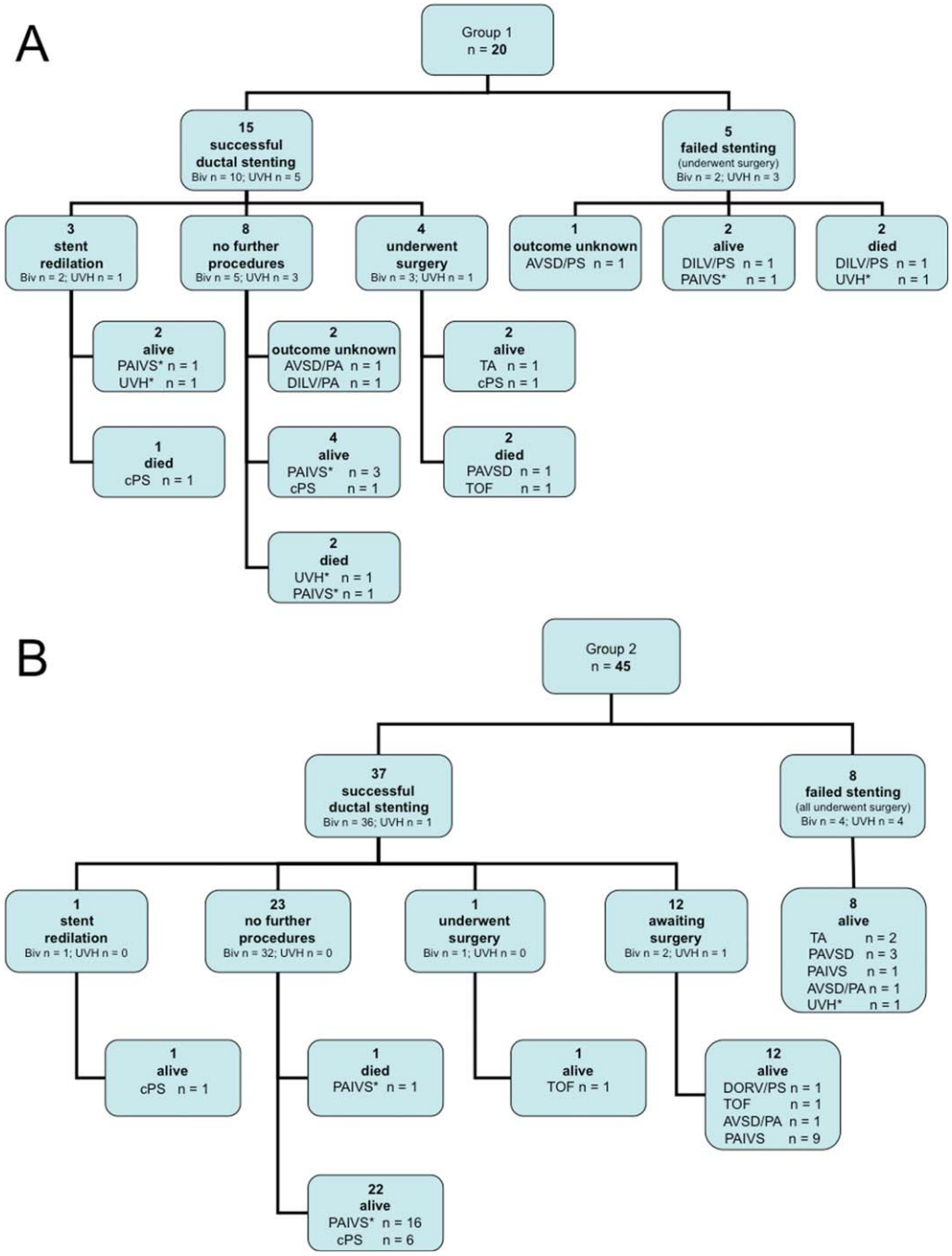

Fig. 3. Flow chart of reinterventions, surgical repair, and clinical outcome of 65 patients in whom ductal stenting was attempted between (A) 1991–2000 (Group 1) and (B) 2001–2009 (Group 2). Abbreviations as in Tables I and II. PAIVS* = representing pulmonary atresia with intact ventricular septum patients undergoing concomitant RF-catheter perforation of the pulmonary valve and balloon dilation; UVH* = other types of univentricular physiology.

Procedural-Related Complications

Complications occurred in 12/52 patients (23.1%). There was no catheter related mortality. More complications were encountered in group 1 (group 1: 7/15 (46.6%) patients, group 2: 5/37 (13.5%), $P = 0.033$). Loss of arterial pulse due to femoral artery occlusion (FAO, $n = 6$, group 1: $n = 3$, group 2: $n = 3$) or axillary artery occlusion ($n = 1$) was the most frequent complication (7/12, 58.3%). Complications were related to the use of a 4F or 5F introducer sheath in the femoral

artery, either to deliver the stent (in the majority of patients the stent was delivered retrogradely via the femoral artery, particularly in group 1), or for aortography. Pulses returned in all infants with intravenous heparin or streptokinase therapy. Other complications included: femoral vessel injury with intimal flap formation ($n = 1$), right pulmonary artery stenosis ($n = 2$) which occurred 2 infants with vertical ducts and a preexisting mild RPA stenosis, due to the stent being oriented towards the proximal left pulmonary artery and exacerbating the RPA stenosis, and necrotising enterocolitis (NEC, $n = 2$). NEC developed within 24–48 hr after DS. One patient had TOF with an isolated left PA, the other infant was diagnosed having PAIVS. Stent diameter was 4.5 mm and 5 mm, and body weight was 3,200 and 3,270 g, respectively. Patients were treated conservatively without subsequent complications.

Ductal Patency

Data on ductal patency during follow-up were available for 34/52 (65.4%) patients. All patients received acetylsalicylic acid for as long as ductal patency was needed. After a median follow-up time of 25 months (range 1.5–156 months), the arterial duct was still patent in 27/34 (79.4%) infants. In seven patients, the duct had: (1) either closed spontaneously during routine follow-up, after cessation of aspirin therapy, as patency of the duct was no longer considered necessary; (2) or been surgically closed during correction of the underlying cardiac defect. Most patients with patent ducts (24/27, 88.9%) underwent DS as part of a catheter-based therapy for PAIVS ($n = 19$) or cPS ($n = 5$). Ductal patency was limited in three patients (all Group 1) due to incomplete coverage of the arterial duct. Two of these patients underwent surgical repair and stent removal 4 months after DS. The clinical outcome of the third patient is unknown.

Primary Surgery Versus Ductal Stenting

To assess the possible impact of DS on the clinical management of PAIVS, we reviewed medical charts to identify all infants with PAIVS. Primary surgery, as opposed to DS, was performed in 21 patients with PAIVS during the same time-scale. Indications for surgery were almost entirely based on the echocardiographic prediction that a biventricular correction was not obtainable (unipartite right ventricle, Ebstein's anomaly of the tricuspid valve with severe regurgitation, extensive right ventricle to coronary artery communications). When any of these findings were confirmed, primary surgery was preferred in two of the centers with appropriate surgical facilities. There was also a tendency to prefer surgery in patients with other forms of univentricular heart and duct-dependent pulmonary circulation in whom the ductal anatomy was considered unfavourable for stenting (tortuous ducts), if surgery was readily available.

Reinterventions, Surgery, and Clinical Outcome

Need for reinterventions, surgical repair and clinical outcome of 65 patients in whom DS was attempted is summarized in a flow chart (Fig. 3). Reinterventions were required in 4/52 patients (7.7%). Stent redilation was needed in three patients due to increasing cyanosis. In one of these patients, the duct was closed using a coil 9 months later. Another patient underwent stent redilation and device closure of an atrial septal defect 18 months after the initial procedure. DS was a bridge to surgical repair in 5 patients (TOF $n = 2$, PAVSD $n = 1$, TA $n = 1$, cPS $n = 1$). Moreover, 12 patients are awaiting cardiac surgery (PAIVS $n = \mathbf{9}$, TOF $n = 1$, AVSD/TGA/PA $n = 1$, DORV/cPS $n = 1$). No further procedures were required after DS in the remaining 40/52 patients (77%). Most of these patients had a diagnosis of PAIVS or cPS.

Follow-up data for longer than 6 months (range 6 months to 13 years) were available for 30/52 patients (57.7%). Some of the patients with good clinical palliation at their last outpatient visit have not achieved 6 months of follow-up; for 2 patients in group 1 who were lost to follow-up, the clinical outcome was unknown. Six patients died (11.5%, Group 1: $n = 5$; Group 2: $n = 1$). Complex cardiac disease was present in four of these patients. Cause of death was unrelated to the DS procedure. One patient died from ventricular fibrillation, 2 days after DS.

DISCUSSION

The present study shows that (1) the success rate of DS in the last two decades was good, (2) technical aspects of DS and patient selection have changed during the last 18 years (3) DS is nowadays a feasible and safe therapy in a subgroup of neonates and infants with duct-dependent pulmonary blood flow, (4) DS has become the primary intervention in neonates with PAIVS requiring prolonged duct patency, and (5) stenting vertical tortuous ducts remains challenging although stenting is possible in some of these patients.

Comparison with Previous Studies

DS was successful in 80% of patients, which is consistent with published reports on this topic (65–

90%)[4–12]. Interestingly, the success rate of this procedure was comparable between the last 2 decades (75% vs. 82%). Although the last 2 decades have seen many technical and procedure-related advances in cardiac catheterization, a higher success rate of DS in suitable patients was not encountered in the last 10 years of our study. A report from the early days of DS, describing a single-center experience of deploying this intervention in 11 infants with duct-dependent pulmonary blood flow (PA and TA) demonstrated a success rate of ~64% [11]. According to other studies, duct morphology was a major determinant for success of DS [7,8,14]. Indeed, our study confirms that duct tortuosity is a technical challenge for stent implantation. Tortuous ducts were seen more often in patients in whom stenting failed. Moreover, duct morphology depended on the type of congenital heart disease. For example, straight tubular ducts were demonstrated in all patients with cPS. On the contrary, duct morphology was tortuous in most patients with SVP and all patients with PAVSD. Nevertheless, another paper from the 1990s, described a 100% success rate of stent implantation, even in patients with complex tortuous shaped ducts [6]. Although comparing success rates of these studies seem limited due to differences in applied techniques and materials, sample size, patient selection, and procedural factors, the vascular access approach was different [6,11].

Vascular Access

The site for vascular access seems an important issue in patients with an arterial duct located along the inner curvature of the aortic arch [6,13,15]. Most of these ducts have a certain degree of tortuosity and may be found in patients with complex congenital heart disease such as single ventricle morphology and PAVSD [6,13,15]. In this setting, the left or right axillary artery access, which was used in only a minority of our patients, may have major advantages when a (tortuous) vertical duct is targeted, although this was not demonstrated in our study [13,15]. This technique should be attempted with caution in smaller and premature newborns; thrombosis of the axillary artery occurred in one of the patients from our series after successful stent deployment.

Procedural Modifications in Patients with Tortuous Ducts

In patients with tortuous ducts, the double-wire technique may increase the success rate of DS. A second stiffer wire is advanced besides the primary softer wire, thereby straightening the tortuous duct and supporting the delivery catheter [12,13]. Schranz et al. demonstrated a 100% success rate in tortuous duct stenting using this double-wire technique [13]. This technique was not used in our study, and may account in part for the difference in success rate of DS. However, it is likely that there are tortuous ducts with multiple sharp bends in different planes which are technically impossible to stent [7,8].

Complications of DS and Stent Size

The complication rate of DS has decreased significantly in the last decade. We encountered a high complication rate (46.6%) in the early days of DS. The number of complications decreased to approximately 13% in recent years. Most papers on this topic have reported a comparable complication rate [6,14]. It is important to notice that complications in our series did not have a major effect on clinical outcome. Moreover, no procedure related death occurred. The most frequent complication was transient FAO, which has been described previously [7,8]. Arterial pulses returned after medical therapy in all cases. Due to the small number of patients with FAO, associated risk factors could not be assessed. Secondly, branch PA stenosis of the right PA developed in 2 patients with vertical ducts and a pre-existing RPA stenosis, which was exacerbated by stent implantation (see above). This complication has been reported previously [7].

Of concern is the development of NEC in two of our patients, which has to the best of our knowledge not been described before in infants after DS. Neonates with congenital heart disease are at a substantial risk of NEC [16,17]. Although the pathogenesis of NEC in neonates with congenital heart disease differs from that of NEC in preterm infants, the exact mechanism has not been fully elucidated [16,17]. Pickard et al. suggested that low-flow mesenteric perfusion resulting from cardiovascular abnormalities, cardiac surgery, and bypass may be the predominant factor in so-called "cardiogenic" NEC [17]. Clinically, both of our patients presented with signs and symptoms of a generous pulmonary blood flow after DS. The stent size (4.5 and 5.0 mm) in these patients might have been too large, resulting in an unfavourable mesenteric blood flow. Recent studies support this hypothesis [5,8]. In one study, all neonates with stent diameters of 4.0 mm initially had excessive pulmonary flow [5]. On the other hand, several studies have used stent diameters of more than 4.5 mm, even up to 6.0 mm [7,9,14,18]. Excessive pulmonary blood flow was reported in

only one patient [7], and none of the infants in these studies developed cardiogenic NEC [7,9,14,18]. Thus, stent diameter alone seems not to predict cardiogenic NEC after DS. This hypothesis is supported by our study. Stent diameter differed significantly between our study groups, with larger stents (diameters of up to 6 mm) being used in the earlier days of DS. However, stents of >4.0 mm were used in both study groups. and NEC was encountered in both eras. Nevertheless, it seems reasonable to conclude that the optimal stent diameter depends on indication of DS, type of congenital heart disease, duct morphology, body size, and anticipated ductal patency. Moreover, the realization that larger stents may lead to overshunting of the pulmonary circulation, associated with longer duration of hospital stay, and need for prolonged medical treatment duration, led to a smaller stent diameter being preferred. Despite this caveat, larger stents continued to be used in the second group if facilities for early surgery (surgical pulmonary valvotomy in patients with expected biventricular physiology, or a bidirectional cavopulmonary connection in patients with univentricular physiology) were limited.

Implanting Multiple Stents

Shorter coronary stents and more stents per patient were primarily implanted in the earlier days of DS. When DS is attempted, great care must be taken to cover the duct completely [8]. Duct constriction, resulting in cyanosis of the patient, may even occur when only a small part of the duct is still uncovered [8,14]. Therefore, it was not uncommon to implant two or even three stents per patient in the earlier days of DS. This view has changed dramatically. Nowadays, it is preferred implanting only one stent with sufficient length covering the whole duct. In our study, additional stents were implanted only in patients with complex duct morphology. This concept is supported by the literature [13].

Patient Selection

Although it is tempting to conclude that innovations in stent, wire and balloon technology has contributed to the safety and feasibility of DS, patient selection might have played a major role as well. Indeed, our study demonstrates that patient selection has changed tremendously during the last two decades. Most patients undergoing DS in the early 1990s were diagnosed having UVH. This is not very surprising because as with any new therapy, it is often applied to critically ill patients in whom it is felt that cardiac surgery is associated with increased risks for complications. This study shows that significantly more neonates with PAIVS underwent DS. In PAIVS, establishing an antegrade flow from the right ventricle to the main pulmonary artery is of upmost importance to achieve a therapeutic basis for a biventricular repair [19–25]. Currently, about two thirds of infants with PAIVS can be managed by cardiac catheterisation using radiofrequency assisted balloon pulmonary valvuloplasty [19–25]. After achieving continuity between the right ventricle and pulmonary artery trunk, ~50% of patients with PAIVS require a systemic to pulmonary artery shunt because of a duct-dependent pulmonary blood flow and persisting cyanosis [19–25]. As was shown in our study, duct morhphology in patients with PAIVS is very suitable for DS (horizontal and straight). DS was successful in 94% of our patients with PAIVS, and this success rate was independent of the era in which DS was performed. Moreover, we found that duct patency in these patients was very good. Therefore, neonates with PAIVS requiring duct patency for mild-moderate RV hypoplasia may benefit the most from DS. Recently, it was demonstrated that concomitant DS at the time of radiofrequency valvotomy is feasible and safe [18,25]. Despite DS having been in use for several years, there are no major studies comparing DS with a surgical aortopulmonary shunt, especially in patients in whom no further interventions may be required (PAIVS or cPS). In this subgroup, in whom ductal anatomy is also likely to be favorable for successful stent implantation, DS is clearly preferable to surgery. Avoiding DS in patients with more complex ducts, in whom the benefits are less obvious, may also result in more widespread acceptance of DS. Newer technical modifications of the procedure in patients with tortuous ducts, may allow safe extension of the procedure to this ductal morphology, which may be relevant in settings where surgical services are not readily available.

Study Limitations

There were several limitations to this study. First and foremost, it was performed retrospectively. Given the limited follow-up data available in many of the earlier patients, we were unable to assess differences in clinical outcome between both study groups. However, data on DS indication, cardiac diagnosis, technical features, materials, duct morphology and patency were complete in most patients. Second, there was no standard DS protocol with regard to materials and techniques, making direct comparisons difficult. The procedure was introduced to one of the centers

relatively late, with the intention of providing clinical palliation for infants who might otherwise have died, due to limited neonatal surgical facilities. On the one hand, one might expect better outcomes in this subgroup, due to the relatively late start and a potential selection bias for candidates in whom the procedure might be expected to be straightforward; on the other hand, patients with complex ducts were deliberately included due to the lack of other therapeutic options. Additional confounding factors in comparing the data between centers include the facts that: (1) one of the centers started with the procedure very early, and accounts for most of the patients in group 1; (2) with increasing experience, there has been a clear trend towards using stents of smaller diameters but of longer length to cover the entire duct, (3) with increased experience, there has also been a clear reduction in the number of patients requiring a second or third stent, (4) a more selective approach to DS has been adopted, with more patients having PAIVS or cPS and straight ducts as their underlying lesion, although this has been partially balanced by the need to implant stents in patients with complex ductal anatomy due to the lack of surgery in one of the centers.

However, the relatively similar results in the participating centers and in various reported DS studies, underscore that excellent results with this percutaneous intervention are highly reproducible. There were no major differences in the technique of DS for group 2 between the centers, with the procedure being introduced by one of the participating interventionalists.

CONCLUSIONS

This is the first study showing the evolution of an interventional catheter therapy. Our multicenter study highlights the efficacy and safety of DS in patients with congenital heart disease and duct-dependent pulmonary blood flow. Although new techniques and learning curve have contributed to better DS possibilities, better patient selection has further improved the safety and feasibility of this therapy.

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