Can ductus arteriosus morphology influence technique/outcome of stent treatment?

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Abstract

Introduction: Results and outcomes of ductus arteriosus stenting vary widely. The aim of this study was to determine whether ductus morphology is associated with different procedural outcome.

Methods: Over an 18-year period, 123 patients presented with ductal dependent pulmonary blood flow. Results were retrospectively assessed based on radiographic anatomic features of the ductus arteriosus:

Group 1: “straight” ductus arteriosus, typically seen in patients with Pulmonary atresia with intact septum (PA-IVS), Group 2: “intermediate” ductus arteriosus as seen in severe pulmonary stenosis (PS)-single ventricle, Group 3: “vertical” ductus arteriosus typically seen in patients with pulmonary atresia-ventricular septal defect, Group 4: ductus arteriosus arising from the aorta to a single lung, Group 5: ductus arteriosus arising from the innominate/subclavian artery to a single lung, Group 6: ductus arteriosus from innominate/subclavian artery to both lungs.

Results: Ductal stenting (DS) was attempted in 98 patients with 99 ducts. Successful stenting was possible in 83 patients. Success of DS was significantly different among the groups (p = .04, F = 5.41). Groups 1, 4, and 5 were “easy” with good success while Groups 2, 3, and 6 were complex and demanding. There were two deaths (after 5 and 7 days, respectively) that could be ascribed to DS. Elective re-interventions were performed in 34 ductuses (40%). Fifty three percent (n = 44/83) of successful ductus stents proceeded to further surgery and 20 ducts closed spontaneously in asymptomatic patients over time.

Conclusions: Ductus arteriosus morphology influences technique and determines complexity, safety, and final outcome of ductus arteriosus stenting.

KEYWORDS
congenital heart disease, cyanosis, ductus arteriosus, ductus arteriosus stent, newborn

INTRODUCTION

Infants with cyanosis and ductus arteriosus dependent pulmonary blood flow usually require an intervention early in life to secure blood flow to the lungs. Complete surgical repair during the neonatal period
is frequently very difficult or may be quite risky. In these cases ductus arteriosus patency is usually maintained by administration of prostaglandins until a systemic to pulmonary artery shunt can be performed.

For years, this approach remained the choice of treatment, but in the late 1990s stenting of the ductus arteriosus offered a percutaneous alternative. Since then this technique has become more refined because of improved technology with low profile stents available in variable lengths and diameters, smaller delivery sheaths and a whole variety of guiding wires leading to a marked improvement in outcome of DS.

Several questions, however, remain unanswered since reports differ widely regarding selection of patients, techniques, and outcomes that vary from good lasting palliation in many to catastrophic procedures in some.

The aim of this study was to determine whether ductus arteriosus morphology influences procedural complexity and outcome.

2 | METHODS

2.1 | Patients

The study was a retrospective review after approval by the UZ Leuven Medical Ethics Committee. The congenital cardiology department of UZ Leuven embarked on a ductus arteriosus stenting program for all patients with ductus dependent pulmonary circulation in 2001. All patients who required a ductus arteriosus stent to secure pulmonary blood flow during the period of February 2001 and February 2018 were included in the study. One hundred and twenty-three (n = 123) newborns were identified. Of these, 25 (n = 25) were directly referred for surgery (preference of parents, referral physician or initially because high tortuosity of the ductus arteriosus).

Patient records and imaging data were used to record demographic and clinical data and captured in an Excel spreadsheet. Data were analyzed using standard statistical software (SPSS for windows, SPSS Inc., IBM company, Chicago, IL, version 18). The one way repeated measurements analysis of variance (ANOVA) test was used to compare outcome data in groups. A p-value <.05 was considered significant.

2.2 | Classification of the ductus arteriosus

Based on clinical experience and technical issues, 6 groups with distinct ductus arteriosus anatomic features were identified, depending on origin from aorta (transverse or descending) or innominate/subclavian artery and course to one or two pulmonary arteries (Figures 1–6).

Group 1: “straight” ductus arteriosus with classic obtuse insertion (<90°) into the thoracic aorta, typically seen in patients with critical pulmonary stenosis (PS) or pulmonary atresia with intact septum (PA-IVS). Although usually straight, some tortuosity may be observed.

Group 2: “intermediate” ductus arteriosus with a more angulated course (90–135°) typically found in severe PS associated with single ventricle morphology. These are usually moderately tortuous and originate lateral to the aorta (usually to the left).

Group 3: “vertical” ductus arteriosus originating from transverse aortic arch. These frequently exhibit tortuosity as is typically seen in patients with extreme tetralogy of Fallot and pulmonary atresia.

Group 4: ductus arteriosus arising from the aortic arch to a single lung (discontinuous pulmonary arteries).

Group 5: ductus arteriosus arising from the innominate or subclavian artery to a single lung, contralateral to the ascending aortic arch (discontinuous pulmonary arteries).

Group 6: ductus arteriosus from innominate/subclavian artery to both lungs (main pulmonary artery).

2.2.1 | Technical aspects

We used the technique as previously described with some modifications over time. Treatment with prostaglandins evolved during the experience. A detailed assessment was made using echocardiography to regulate prostaglandin management and vascular access. Initially all patients were placed on a prostaglandin dosage to obtain good arterial saturations. However, it was observed that patients with straight and sometimes intermediate ductus arteriosus (Groups 1 and 2) often presented at the catheterization laboratory with insufficient ductus constriction to retain a stent. As a result, we adopted the following strategy: after fetal diagnosis, new-borns with this ductal morphology were not immediately started on prostaglandin infusion. The ductus
arteriosus was allowed to moderately constrict until moderate cyanosis (saturation 80%), before prostaglandin was administered. Infusion was stopped on the eve of the procedure, only to be restarted when saturations dropped below 80%. This gave us an idea of the reactivity of the ductus arteriosus, allowing for individualized tailoring of prostaglandin infusion. In contrast, patients with a tortuous duct were always started on prostaglandin from birth: the tortuosity itself does retain the stent, and the stenting procedure is easier/safer with a wide-open ductus. All patients came to the catheterization laboratory with intravenous prostaglandin as well as intravenous ibuprofen available.

Procedures were carried out under general anesthesia. Vascular access technique also evolved with growing experience and became based on ductus arteriosus origin and morphology. After obtaining vascular access, all patients received heparin 50 IU/kg and administration of cefazolin (50 mg/kg). The ductus arteriosus was crossed with a Progreat™ (Terumo Europe N.V. Belgium) micro catheter and positioned as distal in the pulmonary artery as possible. The floppy guidewire of the micro catheter was then exchanged for an extra support 0.014™ coronary guide wire (IronMan™ or Extra Support™ Abbott, Santa Clara, CA). Bare metal coronary stents were initially delivered using a transvenous 6F coronary guiding catheter and subsequently mostly using a 45 cm 4F Flexor arterial or venous introducer sheath (COOK, Bloomington, IN). We aimed to cover the whole length of the ductus arteriosus with a single coronary stent, avoiding significant protrusion into either aorta or pulmonary trunk. The diameter to which the stent was dilated depended on patient weight as described: 3.5 mm in infants 2.5–3 kg, 4 mm stent in

**FIGURE 2** Group 2: Intermediate ductus arteriosus. (a) Intermediate ductus arteriosus with an angulated insertion (90°–135°). The tortuous nature can be seen; also these ductus arteriosus tend to come off quite laterally. Length difficult to judge, but ensuring that the X-ray tube is perpendicular to the ductus arteriosus is helpful—as in (b) of the same patient, tube was turned in a 70° LAO, which demonstrated full length of ductus arteriosus in order to cover both aortic and pulmonary parts of the ductus arteriosus. (c) Successful stent placement

**FIGURE 3** Group 3: Vertical ductus arteriosus. (a) Classical “vertical” ductus arteriosus, tortuous with numerous sharp angles. (b) Successful stent placement via axillary access in order to assist with stent placement; ductal spasm occurs frequently
patients weighing 3 to 5 kg. In the case of the ductus arteriosus supplying only one lung, we selected a stent 0.5-1 mm smaller than that recommended. After the procedure the patients were started on a low dose of acetyl silicic acid $1–2 \text{ mg kg}^{-1} \text{ day}^{-1}$.

Outcomes were defined as follows: The procedure was considered successful if a stent could be delivered into the ductus arteriosus with good pulmonary flow. Failure indicated no possibility of stent placement in the duct. Suboptimal results were defined as those in whom a re-intervention was necessary within 14 days after DS placement either as a result of low blood saturation, inadequate covering of ductal tissue, excessive or asymmetrical pulmonary blood flows.

Patients were followed up until ductal flow was no longer required or patient proceeded to cardiac surgery. Any form of intervention to the stented duct before another surgical palliation or repair or ductal abandon was considered as re-intervention.

### RESULTS

Ninety-eight ($n = 98$) patients with 99 ductuses (one patient had two ducts with discontinuous pulmonary arteries) were catheterized with the aim of DS. The procedure was performed at a median of six (range: 1–83) days. Ductus arteriosus stenting was successful in 83 patients (84%). In 88% ($n = 73/83$) a good result was obtained, while 12% ($n = 10/83$) were considered suboptimal. Failure of DS ($n = 16$) occurred because of inability to cannulate the ductus arteriosus with wire ($n = 13$), inability of stent to enter ductus arteriosus ($n = 2$) or ductus too large to retain the stent ($n = 1$). Success of ductal stenting was significantly different among the groups ($p = .04$, $F = 5.41$); no relation could be found between number of stents required and morphological ductus arteriosus group ($p = .12$, $F = 2.8$).

Demographic, clinical, and procedural information for the individual groups can be viewed in Table 1.
FIGURE 6  Group 6: Ductus arteriosus from innominate/subclavian artery to both lungs. Demonstration of arterial ductus arteriosus in (a) with placement of long stent in (b). (c) Often after removal of catheter and guidewires, kinking of the stent may occur. Difficult to re-engage due to all the angles.

TABLE 1  Outcome of ductus arteriosus stenting

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Note: Unrelated death indicates death before the next percutaneous or surgical intervention.
3.1 | Group 1 (short straight ductus arteriosus) n = 34

All ductus arteriosus in this group were successfully stented (100%). This group consisted mostly of infants with critical pulmonary valve stenosis (PS, n = 21) and pulmonary atresia-intact septum (PA-IVS, n = 13). DS was delayed in five patients due to the ductus arteriosus being too large on arrival at the angiographic suite and was stented during a second session a few days later. Only one patient had a suboptimal result due to uncovered ductal tissue—a second stent was implanted 24 hr later. A single stent gave adequate ductus arteriosus stabilization in 29 patients while five patients required the addition of a second stent at the initial procedure. Access to the ductus was easily achieved via the femoral artery or vein.

3.1.1 | Follow-up

Elective re-stenting was performed in nine patients at an average time of 2 months after the initial procedure. There were three deaths in this group of which only one, who demised after 5 days due to stent thrombosis (autopsy report), was considered related to DS. The other unrelated deaths occurred after 2 and 3 months due to aspiration and multiple congenital abnormalities. Twenty ductuses were left to close spontaneously (59%) after an average of 9.8 months and required no further treatment; two symptomatic ducts were closed percutaneously after 62 and 88 months, respectively.

3.2 | Group 2 (intermediate angle-tortuosity) n = 29

DS was successful in 83% (n = 24/29) of this group. Congenital cardiac abnormalities were mostly complex univentricular type lesions associated with PS or PA-IVS. Ten patients (n = 10) in this group required two stents to cover the length of the ductus. Preferred vascular access was via femoral artery. Three patients had suboptimal results—kinking of stent (n = 1), re-stented; incomplete ductus arteriosus coverage and inadequate pulmonary perfusion (n = 2), requiring central shunts.

3.2.1 | Follow-up

Elective BA (n = 2) and re-stenting (n = 12) were done after 2.8 months and in three a third stent after longer than 6 months was implanted. There were three deaths in this group, of which only one was possibly related to DS—the child demised suddenly at home 13 days after discharge. One died due to sepsis after 5 days and another during induction of anesthesia. Seventeen patients proceeded to surgery at a later age: bidirectional Glenn (BDG, n = 12), correction (n = 4), central shunt (n = 1).

3.3 | Group 3 (vertical tortuous ductus arteriosus) n = 22

DS was successful in 73% (n = 16/22). These were all markedly tortuous and consisted almost exclusively of patients with pulmonary atresia with ventricular septal defect (PA-VSD). Suboptimal results were experienced in four patients: inadequate ductus arteriosus covering in 1, re-stented; poor flow to left pulmonary artery (LPA, n = 3), required surgical shunt to LPA after 24 hr (n = 1). The majority of patients only required one stent to cover the ductus, in only two patients two stents were implanted. Vascular access varied considerably in this group: early we used femoral vein and femoral artery (success, respectively 3/5 and 0/3), but later axillary and carotid arteries were used to gain adequate stable access for DS (success 13/14; p < .01). Once the ductus arteriosus was probed with the micro catheter, insertion of the stiff coronary wire resulted in straightening and spasm of the ductus; a good positioned sheath at the entrance of the ductus was then required to ensure passage of the stent through the ductus arteriosus.

3.3.1 | Follow-up

Elective BA of three stents and re-stenting of three were carried out during follow-up. There was one death after 8 days in this group in an infant who developed sepsis and was Hepatitis B positive. Fifteen children proceeded to surgery: repair (n = 9), BDG (n = 2) and central shunt (n = 4).

3.4 | Group 4 (ductus arteriosus from aorta to single lung) n = 2

Both ductuses were successfully stented. One duct was electively redilated and re-stented to delay repair well beyond 3 years and the other proceeded to corrective surgery (tetralogy repair and re-implantation of pulmonary artery).

3.5 | Group 5 (ductus arteriosus from innominate/subclavian artery to single lung) n = 4

DS was successful in all attempts via mostly the femoral artery. One ductus was severely constricted upon arrival in the catheterization laboratory (Figure 4). One patient required two stents to cover the whole length of the arterial ductus arteriosus. Two patients proceeded to elective surgery and one was re-stented to delay repair beyond 3 years.

3.6 | Group 6 (ductus arteriosus from innominate/subclavian artery to two lungs) n = 5

DS could only be carried out successfully in 60% (n = 3/5) patients. In one a suboptimal result was obtained due to kinking of the stent and
a systemic to pulmonary artery shunt was performed after 4 days. The ductus arteriosus could easily be accessed via the femoral artery, however, these were quite long and minimal stent length used was 20 mm. In one of the failures despite making use of both femoral venous and arterial access, the long stent could not be advanced into the ductus. In another, the straightening of the ductus arteriosus occurred during inflation of the balloon resulting in shifting of the stent in the ductus with it being too long.

3.7 Complications

Only 2 sudden unexplained deaths after 5 and 13 days were considered related to DS and 1 possibly (anesthetic death Group 2). Two patients were referred for emergency surgery required on the day of attempted DS (both in DS failure group of Group 3). During DS, 4 patients developed transient atrioventricular block and three patients a supraventricular tachycardia; all responded to conventional medical treatment. Ductus arteriosus spasm occurred in some patients of Group 2 and most of Group 3 and required prostaglandin infusion and immediate stent placement. No major complications were experienced after the procedure and temporary vascular problems (white limbs) were recorded in two patients after DS. In one of these, percutaneous retrieval of a premounted stent which became displaced from the balloon, damaged the axillary artery but circulation improved after 10 min of initiation of continuous infusion of heparin. One stent thrombosed acutely during a re-dilatation 3 months after implantation; this was successfully treated by placement of a second stent.

3.8 Medium term follow-up

Overall, there were a total of seven deaths and 44 children proceeded to either palliative or reparative surgery. The remainder either did not require further interventions or closed spontaneously (n = 20) or are still in follow up. The longest documented ductus arteriosus stent in our series remained patent for more than 7 years, where after it was closed percutaneously. One 3 year old child with bilateral ducts and discontinuous pulmonary arteries (complex right isomerism) had both stents dilated to 5 mm; we anticipate to delay surgery with creation of central pulmonary arteries for many months.

4 DISCUSSION

Stenting of the ductus arteriosus has evolved as a viable and competitive alternative to surgical systemic to pulmonary artery shunts in patients with ductus arteriosus dependent pulmonary blood flow.8–10 Two recent large multicentre studies have concluded that outcomes of DS are comparable and even superior to the surgical alternative4,5 Odds of survival, pulmonary arterial growth and shorter hospital stay are significantly better in patients with DS. However, after 25 years of DS areas of concern remain and some questions have not been adequately answered.6 A cardiologist embarking on a DS program faces a number of challenges. There is a demonstrable learning curve probably due to the fact that among others, no general well-defined standardized technique exists.11 Numbers of patients treated with DS are also far less than surgical shunt series and marked variability in outcomes are reported in the literature.12–15

The results of our study show that a wide spectrum of ductus arteriosus morphology, origin and varying degrees of tortuosity may be encountered and that it has a significant influence on success and complexity of DS. Patients with subgroup morphology of Groups 1, 4, and 5 were “easy” with high rates of success (100%) while the ductuses in groups 2, 3, and 6 were less successful (60–83%). From a practical perspective, a brief description of each subgroup is warranted.

Our overall success rate of stenting compares favorably to substantial published series who reported success rates which varied between 82 and 93%.4,6,11,16 Group 1 patients were the easiest of the groups when adopting individualized prostaglandin management. Access for initial and subsequent stent placement was generally easy and usually only one stent was required. Group 2 patients frequently had moderately tortuous ducts, but these are relatively easy to engage. Failures were the result of the inability to cover both aortic and pulmonary ends of the ductus arteriosus. The major challenge to overcome was the inability to image the whole length of the ductus arteriosus as these do not arise from the customary anterior position in the aorta; instead, a course more lateral and to the left is followed. In this scenario the problem can be overcome by changing position of the X-ray tube perpendicular to the ductus (e.g., LAO or RAO) in order to visualize both ends in one plane. Once stented, re-stenting did not pose any challenges.

Patients in Group 3 were the most difficult to stent and many consider the vertical ductus arteriosus as a contra indication to DS. Although not always the case, the ductus arteriosus tends to be highly tortuous. During the latter phase of our experience, we adjusted our access techniques and found carotid and axillary access helpful to engage this type of ductus. Ductus arteriosus spasm occurs frequently in this group and may be lethal if the team is not adequately prepared. We always use a micro catheter with a very soft floppy guidewire (Progreat®) to cannulate the ductus. Crossing a tortuous ductus arteriosus and gaining access to the pulmonary artery is difficult and requires a lot of manipulation and at least two pairs of skilled hands. Typically in these, the ductus arteriosus straightens with frequent spasm when the soft guidewire is exchanged for the stiff guidewire to implant the stent.17 One must therefore plan in advance to be able to stent the ductus arteriosus in an emergency and have all equipment ready for example, insufflator & stent. Vascular access plays a pivotal role in this group and because of this, we have changed access to carotid or axillary cannulation—it improves the angles of engagement with the ductus for stent delivery. Other techniques such as using a “buddy”-wire or delivery sheaths/catheters (due to larger profile problematic in small children) may also improve success.

Groups 4 and 5 were reasonably easy to stent, but this usually small ductus arteriosus tended to close rapidly despite administration
of prostaglandins; many of these patients have good oxygenation as the other lung is perfused normally. Consequently, we have changed our management and perform DS in the first 24 hr after diagnosis.

Group 6 patients are quite difficult—the length of stent required to cover the whole length of the ductus arteriosus makes it difficult to traverse the angles of the ductus arteriosus. Once the stent is in position, the angles and length tend to dislodge the stent during balloon inflation—operators should be careful of this. Fortunately, these cases are few, but a self-expanding stent would theoretically allow better tracking, easier delivery and opening with respect to the curvature. Access from a carotid artery might be helpful. Alternatively, a shorter stent could be first placed and the ductus arteriosus covered stepwise since re-engagement of long stents in this position is problematic as they tend to kink the ductus arteriosus which changes the angles at the origin, leaving limited options for re-dilation or re-stenting.

In summary, it is thus clear that morphological variants of the ductus arteriosus have a noteworthy effect on DS technique and management should be tailored accordingly. This is in agreement with a recent study by Qureshi et al., where a significant association was observed between ductal origin and vascular access site.\textsuperscript{18} The study also emphasized the marked variations in tortuosity of the ductus arteriosus and the authors developed a tortuosity index which in essence demonstrated that increasing degrees of tortuosity are associated with increased complexity, confirming our clinical impression. Improvements in access techniques, guidewire and stent technologies will increasingly add to the success of DS.

The 40\% cumulative elective re-intervention rate appears quite high (34/83) but compares well with other studies where it ranged from between 35 and 40\%.\textsuperscript{5,11} Over time flow over the stented ductus arteriosus diminishes due to luminal narrowing for a number of anatomical reasons. Furthermore, relative to somatic growth, the fixed diameter of the stented ductus becomes smaller. Certainly, in our single ventricle program, we aim for a 2-step shunt to avoid initial over shunting early after birth, but give a second wind a few months later with the aim to have maximal catch-up growth of the pulmonary arteries before proceeding to Glenn shunt.\textsuperscript{19} Though some see this as a complication, we consider re-intervention as an elective procedure which is part of a treatment strategy allowing the interventionalist to prevent pulmonary plethora, promote a more balanced growth of the pulmonary arteries and tailor pulmonary flow (and growth) in relation to somatic growth.\textsuperscript{5,20} Therefore, it was not unusual for some patients to have had up to 3 elective re-interventions in our series—in one patient flow was extended beyond 7 years. Re-stenting was favored because of the potential for intimal ingrowth into a previously placed stent. It should be noted that coronary stents could be expanded to almost 5 mm to provide even longer palliation if required: in a patient with bilateral stents and discontinuous pulmonary arteries, we have already delayed surgery by more than 3 years.\textsuperscript{21} Fifty-three percent (n = 44/83) of successful DS proceeded to either reparative or palliative surgery and the rest of patients either did no longer require ductus arteriosus flow anymore or are still in follow-up; this indicates how effective DS is both as temporary palliation or as bridge to surgery.

Complications were limited and no procedure-related deaths occurred in the catheterization laboratory. Only two and one more possible death, which occurred after several days, could be ascribed to DS (3\%). Our complication rates for major and minor complications also compare favorably to other studies in which rates of 8\% and 9–13\% respectively were reported.\textsuperscript{5,11} This should be related to surgical series where procedural complication rates of 21\% and mortality rates ranging from 6 to 13\% have been reported (vs. 6\% of DS).\textsuperscript{4–6,22–24}

## 5 | LIMITATIONS

The fact that 25 patients were sent directly to surgery introduces a selection bias, obviously including some with complex ductus arteriosus. However, as we pointed out, these occurred mostly during the initial phase of the study and included parental and physician preferences. Furthermore, it should be recognized that sheaths, guidewire and stent technology improved markedly over the study period, which undoubtedly had an influence on outcomes. A carotid approach was used in only a few patients, but with more experience, this may make some accesses and interventions easier. The exact number of episodes of ductal spasm was not documented and we mention our subjective clinical experience where it appeared to be more common in certain subgroups. Minor complications may be underreported since these are not always documented.

## 6 | CONCLUSIONS

Not every ductus arteriosus is equal. Ductus arteriosus morphology influences technique and determines complexity, safety, and final outcome of ductus arteriosus stenting. DS is feasible in all types of ductuses but risk varies from low and predictable (Groups 1, 4, and 5) to high risk and poorly predictable (Groups 2, 3, and 6). Management of patients with ductus arteriosus dependent pulmonary blood flow should be individually tailored to the ductus arteriosus anatomy of each patient and experience of the center and operator. Surgery might be a better option in certain high-risk groups.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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