Pediatric pulmonary arterial hypertension
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Pulmonary arterial hypertension in children after neonatal arterial switch operation

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Groningen, the Netherlands; London, the United Kingdom; Denver, Colorado, United States; Paris, France; Sevilla, Barcelona and Madrid, Spain
ABSTRACT

Background-- Pediatric pulmonary arterial hypertension (PAH) after neonatal arterial switch operation (ASO) for transposition of the great arteries (TGA) is a clinically recognized entity with an estimated incidence of 0.6-1.0%. Nevertheless, a clinical characterization is lacking. We present an international cohort of children with PAH after neonatal ASO for TGA and describe epidemiology and clinical course.

Methods-- Data were collected of children with PAH after neonatal ASO (≤6 weeks after birth) for simple TGA without residual shunt-defects, identified in four national pediatric PAH-networks in Europe and one US-referral center.

Results-- Twenty-five children were identified between 1989 and 2014. In 17 children (68%), PAH was detected <1 year after ASO. In the remaining children PAH was detected after median 64 months (IQR 24.5, 94.5). Twenty-four children (96%) received PAH-targeted therapies. During follow-up after ASO (median 5.2 years), 8 children died, 4 underwent lung-transplantation and 2 received a Potts shunt. One- and 5-year Potts shunt- and transplant-free survival after ASO was 100% and 73%. From first PAH-detection this was 100% and 58%, respectively, which did not differ between children with early (<1 year after ASO) or late PAH-detection.

Conclusions-- The occurrence of PAH after ASO for TGA represents a specific association. PAH-onset may be early or late after ASO, with similar fatal course from first PAH-detection. Mechanisms leading to PAH in this association are unknown, but may include abnormal prenatal pulmonary hemodynamics and/or genetic susceptibility. Routine, lifelong follow-up for children who undergo ASO for TGA should include screening for PAH.
INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare and progressive disease of the pulmonary vasculature and has a poor prognosis.¹ In children, PAH has an estimated annual incidence rate of approximately 3 cases per million children and is most frequently idiopathic or associated with congenital heart disease (CHD).¹,² CHD in PAH typically includes the presence or history of a shunt-defect, as increased pulmonary blood flow is believed to trigger the remodelling of small pulmonary arteries that is characteristic for PAH.³ However, PAH has also been reported in children with CHD other than shunt-defects.²,⁴

Transposition of the great arteries (TGA) is one of the most common cyanotic CHD, contributing to approximately 5% of all CHD.³ Early development of severe pulmonary vascular disease (PVD) has been well recognized in patients with uncorrected TGA.⁶,⁷ With its occurrence reported already in the first weeks of life, PVD in TGA seems to develop more rapidly than in other types of CHD.⁷,⁸

In earlier days, surgical management for TGA consisted of functional repair with an atrial redirection procedure (the Mustard or Senning procedure). These procedures were usually performed in the second half of the first year of life or even later, resulting in long-term presence of cyanosis and shunt-lesions. Consequently, PAH is a well-recognized late complication of these procedures and has been reported to occur in approximately 7% of patients who survive into adulthood.⁹

Since the 1980s the arterial switch operation (ASO) has become the treatment of choice for simple TGA.¹⁰ This procedure, in which the pulmonary artery and aorta are literally switched and the coronary arteries reimplanted, provides an anatomical repair and has a very good prognosis.¹¹ The operation is usually performed within the first 2 weeks of life, precluding the presence of a long-term shunt-lesion as a trigger for the development of PAH in patients with TGA.

Nevertheless, the association of PAH and TGA, also after a successful neonatal ASO, has been clinically recognized in pediatric pulmonary hypertension (PH) centers. An explanation for this association is unknown, but proposed mechanisms include programming of endothelial dysfunction due to prenatal hypoxic or postnatal hyperoxic blood perfusing the pulmonary vasculature in uncorrected TGA, genetic susceptibility, abnormal bronchial circulation and the dispersion of microthrombi, for instance during atrial balloon septostomy.¹²-¹⁴

To date, however, a clinical characterization of presentation, risk factors and prognosis of this entity is lacking. With the current study, we aim to characterize this clinical entity by presenting an international cohort of children with PAH after neonatal ASO for TGA and describing its epidemiology and clinical course.
METHODS

This study is a retrospective, international multicenter study. Children with PAH and TGA repaired in the neonatal period with ASO between 1989 and 2014 were identified from nine dedicated pediatric PH centers in Europe and the United States, including four national registries (United Kingdom, France, Spain and the Netherlands). Ethical approval for the registries was obtained from the institutional review boards (of the constituent/participating registries) and the participants or their guardians provided written informed consent at enrolment.

Neonatal correction was defined as ASO within six weeks after birth. To exclude PAH associated with shunt-defects, only patients with no hemodynamically relevant residual shunt-defects after ASO were included in this study.

Patients and data collection

Patient characteristics were collected from patient charts including gestational age, sex, medical history, the presence of other possible PAH associated conditions and anatomical cardiac diagnosis. Only children with no hemodynamically relevant residual lesions were included, thus only patients with isolated TGA or TGA associated with a ventricular septal defect (VSD) that had been successfully closed during ASO. Also, children with residual pulmonary branch stenosis or impaired left ventricular function were not included in this study. Parameters regarding the ASO and post-operative phase included whether there were any PAH-relevant complications and/or pulmonary hypertensive crises peri-ASO.

PAH was confirmed by cardiac catheterization in all but 1 patient. PAH was defined as a mean pulmonary artery pressure ≥25 mmHg with a mean pulmonary capillary wedge pressure ≤15 mmHg. In one child mean pulmonary capillary wedge pressure was not available at cardiac catheterization and another child had an echocardiographic PAH diagnosis. In both children left heart disease was excluded by echocardiography on review of the center's expert physician. The age of first PAH detection, either with echocardiography or cardiac catheterization, was determined.

Treatment information included the use of supportive therapies, PAH-targeted therapies (including endothelin receptor antagonists, type 5 phosphodiesterase inhibitors and prostanoids) and surgical interventions during follow-up, i.e. atrial balloon septostomy, Potts shunt or lung transplantation. Treatment intensity was defined as the number of PAH-targeted drugs at endpoint or last follow-up (PAH-targeted mono-, dual or triple therapy).
Statistics

Data are presented as number (percentage) or median (interquartile range) when appropriate. The first occurrence of Potts shunt, lung transplantation or death was defined as the primary endpoint in this study. Patients who did not die nor received a Potts shunt nor underwent lung transplantation were censored at the last follow-up visit. Potts shunt- and transplant-free survival was depicted using Kaplan-Meier curves. Differences in survival were explored using the log-rank test. P-values <0.05 were considered significant.

RESULTS

Patients

In total, 25 children with PAH and neonatal ASO for TGA were identified (Table 1). All children were born after a gestational age of at least 36 weeks. Most children (76%) were males. Nineteen children (76%) had an intact ventricular septum and six had a concomitant VSD (Table 2). Four children (17%) had a history of perinatal asphyxia. Three (13%) had associated persistent pulmonary hypertension of the newborn (PPHN). One of whom required peri-operative extracorporeal membrane oxygenation. No recognized comorbidities, syndromes or dysmorphic features were reported, except for epilepsy and hydrocephalus associated with perinatal asphyxia in one child. No other causes for or conditions associated with PAH were identified in any of the children.

Table 1. Participating networks/centers and number of patients

<table>
<thead>
<tr>
<th>Continent</th>
<th>Network / Center</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>Europe</td>
<td>The National Paediatric Pulmonary Hypertension Service United Kingdom</td>
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</tr>
<tr>
<td></td>
<td>Great Ormond Street Hospital for Children, London, United Kingdom</td>
<td></td>
</tr>
<tr>
<td></td>
<td>French Pediatric Pulmonary Hypertension registry</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Necker Hospital for Sick Children, Paris, France</td>
<td></td>
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<tr>
<td></td>
<td>The Dutch National Referral Center for Pulmonary Hypertension in Childhood</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Beatrix Children’s Hospital, University Medical Center Groningen, the Netherlands</td>
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<tr>
<td></td>
<td>The Spanish registry for Pediatric Pulmonary Hypertension (REHIPED)</td>
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<tr>
<td></td>
<td>University Hospital Ramon y Cajal, Madrid, Spain</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>University Hospital Doce de Octubre, Madrid, Spain</td>
<td>2</td>
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<td></td>
<td>University Hospital Virgen del Rocio, Seville, Spain</td>
<td>1</td>
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<tr>
<td></td>
<td>University Hospital Vall d’Hebrón, Barcelona, Spain</td>
<td>2</td>
</tr>
<tr>
<td>United States</td>
<td>Children’s Hospital Colorado, Aurora, Colorado</td>
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Twenty-one children (84%) underwent an atrial balloon septostomy in the first days of life. Median age of ASO was 8 days. Four children had a small (residual) VSD after ASO, considered not hemodynamically relevant.

At first cardiac catheterization post-ASO median mean pulmonary artery pressure was 48 mmHg and median indexed pulmonary vascular resistance was 11.5 Wood units.m² (Table 3).

**Time of PAH detection**

Median age at first PAH detection was 3 months (IQR 1, 14) with a range of 1 to 137 months (Table 3). In fact, PAH was detected within one year after ASO in 17 children (68%) with a median age at first PAH detection of 1.5 months (IQR 1, 3). In the remaining 8 children median age at first PAH detection was 64 months (IQR 19.5, 94.5). Patient and disease characteristics, as shown in Tables 2 and 3, did not differ between these two groups. All three children with PPHN had first PAH detection within one year after ASO.
Follow-up
Median follow-up after ASO was 5.1 years (IQR 2.9, 12.1). During follow-up, two children received a Potts shunt, four children underwent lung transplantation and eight children died. Of the eight deceased children, five died of progressive right ventricular failure, one of massive hemoptysis and two died during a follow-up cardiac catheterization, one of whom during atrial balloon septostomy procedure for PAH. One-, 3-, 5- and 10-year Potts shunt- and transplant-free survival rates after ASO were 100%, 82%, 73% and 65%, respectively (Figure 1). From first PAH detection these were 100%, 73%, 58% and 50%, respectively.
Potts- and transplant-free survival from ASO of children with first PAH detection within one year after ASO was worse than survival of those with first PAH detection more than one year after ASO (p=0.039, Figure 2A). However, survival from first PAH detection did not differ between these two groups (p=0.409, Figure 2B).

During follow-up, four children underwent atrial balloon septostomy for treatment of PAH. Fourteen children (50%) received supportive therapies, including anticoagulation, diuretics and/or oxygen treatment. One child was on calcium channel blocker monotherapy after the parents had refused intravenous epoprostenol therapy, while other PAH-targeted therapy was not available at that time. Six children (24%) received PAH-targeted mono-, 8 (32%) dual and 10 (40%) triple therapy (Table 3).

Of the 11 children that did not die, neither underwent lung transplantation nor received a Potts shunt during follow-up, three children were in World Health Organization functional class (WHO-FC) I, 7 in WHO-FC II and one in WHO-FC III at last follow-up (median time from first PAH detection 4.4 years [IQR 1.8, 5.1]).
Figure 2. Potts shunt- and transplant-free survival of children with first PAH detection within and more than one year after ASO

A. Survival from ASO. One-, 3-, 5- and 10-year survival was 100%, 74%, 59% and 40% for the 18 children with first PAH detection within one year after ASO and 100%, 100%, 100% and 100% for the 7 children with first PAH detection more than one year after ASO, respectively (p=0.039).

B. Survival from first PAH detection. One-, 3-, 5- and 10-year survival was 100%, 75%, 60% and 45% for the 18 children with first PAH detection within one year after ASO and 100%, 71%, 57% and 57% for the 7 children with first PAH detection more than one year after ASO, respectively (p=0.409).

ASO, arterial switch operation; PAH, pulmonary arterial hypertension; TGA, transposition of the great arteries.
DISCUSSION

The current study describes a cohort of 25 children with a specific association: children with TGA that developed severe, progressive PAH after timely and successful ASO and in the absence of hemodynamically relevant residual lesions. PAH could present already very early after ASO, but also late, after several years. Despite the intense use of PAH-targeted therapies, Potts shunt- and transplant-free survival in this cohort was poor with a 5-year survival rate of 73% after ASO and 58% after first PAH detection. In these children, in whom ASO was performed at a median age of 8 days, there was no long-term shunting as trigger for the development of PAH. Therefore, these patients challenge the general concept of PAH associated with CHD, in which prolonged exposure to increased pulmonary blood flow due to a shunt-defect is considered the trigger for the development of advanced and irreversible pulmonary vascular remodelling.

Incidence of PAH after neonatal ASO for TGA

For this study, the total number of ASOs for TGA performed at each participating center or within each national cohort during the study period was not available. Therefore, the design of this study precluded the determination of an incidence rate of the association of PAH after successful neonatal ASO for TGA. After conscientiously studying the literature regarding PAH and ASO for TGA, we identified cases of PAH during follow-up in cohorts of children that underwent neonatal ASO for TGA. Out of 100 ASO procedures, Rivenes et al. described one child who underwent ASO at age 4 days and developed PAH at the age of 42 months.15 In a series of 156 patients, Losay et al. mention one patient with PAH after ASO at the age of 2 weeks.16 Cordina et al. describe a patient who underwent ASO for simple TGA in the neonatal period and presented with PAH at the age of 16 years.17 Since the latter study included only patients ≥17 years of age, it was not included in incidence estimation. Finally, Roofthoof et al. identified one patient with PAH (included in the current study) from a consecutive series of 112 ASO-patients.18 From these data, it can be roughly estimated that PAH after neonatal ASO for TGA may occur in 0.6-1.0% of the cases. This estimated incidence, based on literature review, precludes a merely coincidental concurrent occurrence of idiopathic PAH and TGA. The true incidence of the concurrence of TGA and PAH may be even higher since no systematic screening program for PAH after ASO has been reported and consequently patients with PAH might have been missed. Furthermore, prenatal or early severe PVD may cause children with TGA to die even before they undergo ASO.19
Clinical characterization

The male predominance observed in this cohort is in contrast to the generally observed female predominance in pediatric PAH. This can be explained by the reported overall male predominance in TGA.

In this cohort, we identified children with early-onset PAH, e.g. first PAH detection within one year after ASO, and children with late-onset PAH who had first PAH detection several years after ASO. Survival from ASO was better in this latter group, intrinsically associated with its definition. The observation that survival from first PAH detection did not differ between both groups implies that the PAH in the late-onset group actually developed later in life than in the early-onset group, instead of simply being detected later. Therefore, early- and late-onset PAH may represent two different phenotypes and we hypothesize that both phenotypes may be part of the spectrum of PVD associated with abnormal prenatal hemodynamics in TGA. We were not able to identify discriminating clinical characteristics in the early- or late-onset patients.

In the current clinical classification for PH, Nice, 2013, PAH associated with CHD is classified based on shunt status. Since neonatal ASO for TGA precludes the presence of long-term postnatal shunting, such classification is not suitable. It has been previously advocated that pediatric PVD has specific aspects that are not sufficiently covered in the current classification for PH, including insults on developing and growing organs. The clinical entity described in this manuscript illustrates the need for further “pediatric adaptations” of the current classification, with special attention for CHD other than shunt lesions and for the concept of programming due to pre- or postnatal abnormal conditions.

After first PAH detection, prognosis was poor and comparable to that of children with idiopathic PAH in the current era. This is in sharp contrast to the excellent long term survival after ASO reported to be around 98% after 15 years, with approximately 80% freedom from reintervention. Thus, this study shows that the occurrence of PAH early or late after ASO represents an important prognostic factor that significantly worsens prognosis. Therefore, the authors advocate that routine lifelong follow-up for children who undergo ASO for TGA should include screening for PAH to allow for early treatment initiation.

Although the proportion of children receiving PAH-targeted dual and especially triple therapy in this study is relatively high compared to what has been previously reported, a more aggressive and goal-oriented treatment strategy with early use of PAH-targeted combination therapy, as has been suggested for idiopathic PAH, seems to be justified also in these children.
**Underlying mechanisms**

Alterations in prenatal pulmonary hemodynamics have been reported in foetuses with TGA including restriction or closure of the foramen ovale or ductus arteriosus. It has been suggested that such foetal alterations are associated with altered prenatal flow-and mixing-patterns resulting in hypoxia of the prenatal pulmonary circulation and increased bronchial circulation. These alterations may contribute to the development of PVD, already prenatally, in foetuses with TGA. These foetuses are then at risk for rapid postnatal deterioration and death and also for developing postnatal PH. These prenatal hemodynamic alterations may injure or program the developing pulmonary vasculature leading to abnormal postnatal responses. For the current study, foetal echocardiography data were not available. However, 84% of included children underwent an atrial balloon septostomy procedure in the first days of life. This proportion contrasts with the reported incidence of approximately 40% atrial balloon septostomy procedures in infants with TGA, suggesting that incomplete mixing and prenatal hemodynamic changes were more prevalent in these children. Also, the occurrence of PPHN, a condition of disturbed adaptation of the pulmonary vasculature to post-natal life, is more frequent in children with TGA than in the normal population, supporting this concept of altered prenatal pulmonary hemodynamics. PPHN has been suggested to be associated with abnormal pulmonary vascular responses and the development of PAH later in life. In the current study, three children (13%) had PPHN. In a series described by Roofthooft et al., 14 of 112 infants with TGA presented with PPHN, of which 4 died preoperatively. One of the 10 children with PPHN that did undergo ASO developed PAH during follow-up (10%). We hypothesize that the abnormal prenatal hemodynamics in TGA program the pulmonary vasculature leading to a spectrum of PVD including PPHN and PAH that may develop early (pre- or perinatally) or later in life.

Another potential explanation could be that a specific genetic make-up in patients with TGA predisposes for the development of PAH. Known PAH-related genes, such as bone morphogenetic protein type II receptor, have been explored for mutations in patients with PAH associated with CHD, but so far no such mutations have been shown in TGA. However, very recently several candidate genes for TGA were identified. Two of these genes, ACKR3 (or CXCR7) and NF1, have also been associated with endothelial dysfunction, pulmonary vascular remodelling and the development of PVD/PH.

**Strengths and limitations**

This study is the first to characterize occurrence, presentation and clinical course of PAH in children after neonatal ASO for TGA. As such, this study identifies this specific clinical entity and provides clinically relevant information regarding its clinical features. The data are derived from 9 large pediatric cardiology centers, including 4 European national registries, enhancing epidemiologic strength and data quality.
The retrospective nature of the study is associated with inherent limitations. Patients with PAH after ASO might have been missed. Data regarding the total number of ASOs performed in the participating centers or national cohorts during the study period were not available precluding the determination of an incidence rate of PAH after neonatal ASO for TGA from this study. Also, we could not compare children who developed PAH with children who did not, precluding the identification of risk factors for the development of PAH after neonatal ASO for TGA. In the current study perinatal asphyxia was described in 17% of the children and might have played a confounding role in the observed association of PAH and neonatal ASO for TGA. The current study does not allow to identify underlying mechanisms for the development of PAH in patients with TGA after ASO, and consequently, we can only speculate in this regard and provide supportive clinical data. Further research is needed to confirm the hypotheses regarding abnormal prenatal hemodynamics and genetic susceptibility.

Conclusions

Although PAH after successful neonatal ASO for TGA has been clinically recognized as a specific disease entity, the current study is the first to clinically characterize this association. In this cohort, two phenotypes could be distinguished: early-onset PAH, presenting weeks to months after ASO, and late-onset PAH, presenting years after ASO. In both phenotypes, prognosis is poor, despite the intense use of PAH-targeted therapies, and comparable to pediatric idiopathic PAH. This observational study did not allow for the identification of risk factors for the development of PAH after ASO for TGA. We speculate on the role of altered prenatal pulmonary hemodynamics in TGA, including abnormal flow- and mixing-patterns associated with prenatal presence of restrictive foramen ovale and ductus arteriosus, and of genetic susceptibility in these children. The data from the current study imply that routine, lifelong follow-up of children who underwent ASO for TGA should include screening for PAH in order to allow for early treatment initiation.

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