Management and Outcomes of Heterotaxy Syndrome Associated With Pulmonary Atresia or Pulmonary Stenosis

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Background. Historic outcomes of patients with heterotaxy and pulmonary atresia or pulmonary stenosis (PA/PS) have been poor and in the current era are incompletely described. We reviewed our management of these patients and associated risk factors for death.

Methods. We retrospectively reviewed the records of all patients with heterotaxy and PA/PS treated in our institution from January 1, 2002, to August 31, 2012. Death data were also confirmed with the Social Security Death Index. The log-rank test was done to assess six risk factors for death.

Results. We identified 42 patients with heterotaxy and PA/PS. Median age at the first operation was 6.5 days, and median follow-up was 3.5 years. Death data were complete for all patients. Overall mortality was 19% (8 of 42).

The 30-day, 1-year, and 5-year mortality estimation was 4.76%, 12.3%, and 19.1% respectively, as determined by the Kaplan-Meier method. The log-rank test showed total anomalous pulmonary venous return (TAPVR) (p < 0.05) and obstructed TAPVR requiring an operation at less than 30 days (p = 0.001) were significant risk factors for death.

Conclusions. In the current era, surgical treatment of heterotaxy and PA/PS can result in good outcomes. Associated TAPVR and obstructed TAPVR requiring neonatal correction were noted to be risk factors for death.

Patients

Between January 1, 2002, and August 31, 2012, 42 patients with heterotaxy syndrome and PA/PS were treated at Children’s Medical Center Dallas. We performed a retrospective review of the medical records of all patients with heterotaxy and PA/PS. Death data were also confirmed with the Social Security Death Index. The duration of follow-up was calculated from the first operation to the last clinical encounter with a cardiologist at our institution.

Heterotaxy syndrome was defined as a complex of anomalies of visceral-cardiac relations in association with intracardiac pathology [1]. After the initial discharge, most of these patients were managed on a single-ventricle palliation pathway, with the final destination being a Fontan circulation. Follow-up after completion of the Fontan circulation was done at the discretion of the patient’s cardiologist. Patients with associated total anomalous pulmonary venous return (TAPVR) underwent neonatal pulmonary vein repair if they had two or more of the following: clinical signs of obstructed pulmonary veins, chest radiographic evidence of obstructed pulmonary veins, or echocardiography/catheter based evidence of obstructed pulmonary veins.
### Statistical Analysis

The log-rank test was performed to assess the following variables as risk factors for death: discontinuous pulmonary arteries, TAPVR, atrioventricular septal defect, and double-outlet right ventricle (DORV). Patient demographics and associated diagnoses are listed in Table 1. Figure 1 shows the algorithm we use in the treatment of these patients, and Figure 2 summarizes the subgroups within our entire patient cohort.

The median age at the first operation was 6.5 days (range, 1 to 277 days), and median follow-up was 3.5 years (range, 0.06 to 18.5 years). Death data were complete for all patients. The Society of Thoracic Surgeons (STS) mortality for the entire cohort was 11.9% (5 of 42 patients) and overall mortality was 19% (8 of 42 patients). The Kaplan-Meier survival curves in Figure 3 show 30-day, 1-year, and 5-year survival of 95.24%, 87.7%, and 80.9%, respectively.

Among the variables analyzed by log-rank test, the risk factors for death among the entire cohort were the presence of TAPVR and the presence of obstructed TAPVR requiring surgery at less than 30 days of age (Figs 4, 5).

Three patients underwent biventricular repair. Biventricular repair was undertaken in the presence of 2 ventricles of adequate volume and function, as well as a septatable atrioventricular valve with adequate inlet to each ventricle and venoatrial connections.

### Results

We identified 42 patients with heterotaxy and PA/PS. Concomitant diagnoses included unilaterally or bilaterally discontinuous pulmonary arteries, TAPVR, atrioventricular septal defect, and double-outlet right ventricle (DORV). Patient demographics and associated diagnoses are listed in Table 1. Figure 1 shows the algorithm we use in the treatment of these patients, and Figure 2 summarizes the subgroups within our entire patient cohort.

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Three patients transitioned from single-ventricle palliation to the transplant list for failing single-ventricle physiology. Only 1 of these 3 patients received a transplant. The remaining patients have been taken down the single-ventricle palliation pathway with the addition of a TAPVR repair if the pulmonary veins appear obstructed based on chest roentgenogram, clinical examination, and echocardiographic or catheterization diagnosis of obstruction.

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**Fig 2.** Clinical management of heterotaxy with pulmonary atresia/pulmonary stenosis. (TAPVR = total anomalous pulmonary venous return.)

**Fig 3.** Kaplan-Meier survival curve (blue line) is shown with the 95% confidence limits (range bars), with circles indicating censored patients.

**Fig 4.** Survival comparison is shown between heterotaxy patients with pulmonary atresia/pulmonary stenosis with total anomalous pulmonary venous return (TAPVR; dashed red line; red circles indicating censored patients) and those without TAPVR (solid blue line, blue circles indicating censored patients). Log-rank test showed significantly worsened survival in the TAPVR group ($p = 0.038$). The range bars show the 95% confidence limits.
Unplanned Intervention in the Operating Room or Catheterization Suite

Eleven patients required unplanned reintervention in the operating room or in the catheterizer laboratory. The diagnoses, intervention, indication for intervention, and current disposition are listed in Table 2.

Ductal Stent

Ductal stenting was considered in 5 patients and was completed in 2. Three patients did not have favorable ductal anatomy to allow ductal stenting and underwent systemic-to-pulmonary artery shunt placements. In the remaining 2 patients, ductal stenting was performed, followed by TAPVR repair at 8 and 9 months, respectively.

Discontinuous Pulmonary Arteries

Seven patients had discontinuous pulmonary arteries, of which 5 had bilateral discontinuous pulmonary arteries. Three of 5 had unifocalization with central pulmonary artery reconstruction, of whom 1 patient had ductal stents as a neonate. One of these patients, who also had a neonatal TAPVR repair with unifocalization to a modified Blalock-Taussig shunt, died in the perioperative period.

Table 2. Unplanned Intervention in the Operating Room or Catheterization Suite

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Unplanned Reintervention</th>
<th>Indication</th>
<th>Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete AVSD, TAPVR, bilateral SVC, pulmonary atresia</td>
<td>Revision of systemic to pulmonary artery shunt</td>
<td>Inflow stenosis</td>
<td>Awaiting Glenn</td>
</tr>
<tr>
<td>Dextrocardia with unbalanced AVSD, discontinuous pulmonary arteries, TAPVR, bilateral SVC, pulmonary atresia</td>
<td>Pre Glenn LPA stent</td>
<td>Diffusely hypoplastic LPA</td>
<td>Awaiting Fontan</td>
</tr>
<tr>
<td>Unbalanced AVSD, pulmonary atresia, interrupted IVC</td>
<td>LPA stent</td>
<td>Ductal coarctation</td>
<td>Awaiting Fontan</td>
</tr>
</tbody>
</table>
| Dextrocardia with unbalanced AVSD, pulmonary stenosis | • Stenting of right modified BT shunt | • Shunt thrombosis
• Pericardial window | Completed Fontan circulation
• Pulmonary patch arterioplasty | • Pericardial effusion
• Ectopic atrial impulse | • Cyanosis after Glenn
• Ectopic ventricular impulse | • Sternal infection
• Sternal exploration | • Pleural effusion
• Pleurodesis |
| Complete AVSD with pulmonary atresia, obstructed TAPVR | ECMO for respiratory insufficiency | Respiratory insufficiency | Death |
| Unbalanced AVSD, d-malposed great arteries, pulmonary atresia, bilateral SVC | AV valve repair | AV valve regurgitation | Completed Fontan circulation |
| Pulmonary atresia, right aortic arch | ECMO | Postoperative ventricular fibrillation | Death |
| Dextrocardia, DORV with pulmonary stenosis, bilateral cavae, obstructed TAPVR, right aortic arch | ECMO and shunt thrombectomy | Shunt thrombosis | Death |
| Dextrocardia with AVSD, pulmonary atresia, right aortic arch | Shunt revision and arterioplasty | Right pulmonary artery stenosis | Completed Fontan circulation |
| Unbalanced AVSD with pulmonary stenosis, obstructed TAPVR | Pulmonary vein repair | Right lower pulmonary vein stenosis | Awaiting transplant |
| DORV, d-malposed great vessels, bilateral SVC, interrupted IVC, pulmonary stenosis | ECMO and stenting of shunt | Shunt thrombosis | Completed 2-ventricle repair |

AV = atrioventricular; AVSD = atrioventricular septal defect; BT = Blalock-Taussig; DORV = double-outlet right ventricle; ECMO = extracorporeal membrane oxygenation; IVC = inferior vena cava; LPA = left pulmonary artery; SVC = superior vena cava; TAPVR = total anomalous pulmonary venous return.
from morbidity related to malignant supraventricular tachycardia. Of the remaining 2 in the unifocalization group, both underwent superior cavopulmonary connection and are awaiting completion of Fontan circulation. The remaining 2 patients with discontinuous PAs underwent creation of “classic-style” autologous systemic-to-pulmonary shunts with subclavian and unilateral carotid artery turndowns to the ipsilateral pulmonary artery, and both have undergone completion of superior cavopulmonary connection and are awaiting Fontan completion (Figures 6 and 7).

Pulmonary Stenosis
PS was present in 17 patients (40.5%) rather than PA. This did not confer a survival benefit in the log-rank test. Twelve of 17 PS patients underwent systemic-to-pulmonary artery shunts to supplement pulmonary artery blood flow. Of these, 4 had additional control of antegrade pulmonary blood flow with pulmonary artery ligation (n = 1) and pulmonary artery banding (n = 3) after performance of a shunt. We have a low threshold to perform mechanical restriction of antegrade pulmonary blood at the time of systemic-to-pulmonary artery shunt to optimize systemic perfusion. Four patients with PS did not have an initial systemic-to-pulmonary artery shunt.

Two of these had primary bidirectional Glenn, and the other two had TAPVR repair, followed by bidirectional Glenn, without the need for an intervening procedure for additional pulmonary blood flow.

Total Anomalous Pulmonary Venous Return
Associated TAPVR was present in 13 patients, comprising 5 supracardiac, 4 infracardiac, and 4 cardiac-level TAPVR. Of the 5 supracardiac TAPVR patients, 3 had a vertical vein to a right sided superior vena cava, 1 to the innominate, and 1 to a left-sided superior vena cava. Five presented with obstruction and were repaired at less than 30 days of age. Another 4 patients underwent repair at greater than 30 days of age. Of these 4 who underwent delayed pulmonary vein intervention, three had presented with some signs of obstruction but were selected for observation and delayed pulmonary vein repair according to our selection criteria mentioned in Patients and Methods. Obstruction has not developed in 4 patients, all of whom had cardiac level TAPVR, and they have not required any intervention. Only 1 patient has required surgical reintervention for pulmonary vein stenosis.

Comment
To the best of our knowledge, this is the first report dedicated to an analysis of patients with heterotaxy syndrome and PA/PS. Our therapy for these patients has evolved over time. More recently, we have started evaluating these patients for the use of a ductal stent as the
initial neonatal intervention, especially in those with associated TAPVR. We have also adopted a different approach to TAPVR diagnosed in the neonatal period in patients with heterotaxy and PA or PS. A broad-based diagnostic evaluation is performed in neonates with associated TAPVR, looking at the pulmonary vein echocardiographic characteristics or appearance in the catheterization laboratory, chest radiographic findings of pulmonary vein obstruction, and clinical examination findings of pulmonary vein obstruction. Neonatal TAPVR repair was, in general, performed in the presence of two or more factors suggesting obstruction.

None of the cardiac-level TAPVR patients required any pulmonary vein interventions. The extracardiac TAPVR patients who were not repaired in the neonatal period continued to have mild degree of pulmonary vein obstruction beyond the neonatal period. Single-ventricle physiology was present in most of these patients with extracardiac TAPVR and so they underwent pulmonary vein repair to maintain an optimal pulmonary vascular bed.

Other series have reported heterotaxy syndrome in association with univentricular repair [2,3], biventricular repair [4], TAPVR repair [5,6] and right atrial isomerism or left atrial isomerism [7–10]. Right atrial isomerism has been associated with worse survival than left atrial isomerism [7–10]. We did not use atrial isomerism to subclassify our patient population, although we did look at the association with TAPVR, discontinuous pulmonary arteries, PA vs PS, and univentricular or biventricular repair.

Historical outcomes with heterotaxy syndrome and congenital heart disease have been unsatisfactory. Sadiq and colleagues [7] reported 45% overall survival in 20 patients with right atrial isomerism, and only 9 patients were eventual Fontan candidates. Hashmi and colleagues [8] reported a 69% mortality rate for children with right atrial isomerism, and another study from the same institution reported 44% mortality in children born with left atrial isomerism [9].

In 2009, Anagnostopoulus and colleagues [10] reported improved surgical outcomes in heterotaxy patients. In patients with right and left atrial isomerism, 3-year survival was 79% and 94%, respectively. The incidence of sinus node dysfunction was higher in the patients with left atrial isomerism. The risk factors for death in patients with right atrial isomerism were the presence of obstructed TAPVR and greater than moderate atioventricular valve regurgitation. The incidence of single-ventricle palliation was 85% in that series, which is highly comparable to the 93% incidence in our patient cohort. We have found similar risk factors for increased death—the presence of TAPVR and obstructed TAPVR requiring surgical intervention at less than 30 days of age. Ola and colleagues [11] reported their surgical outcomes in patients with right atrial isomerism and also found neonatal palliative intervention to be a risk factor for early death.

Morales and colleagues [6] compared the outcomes of TAPVR repair in patients with and without heterotaxy. With a mean follow-up of 2.6 years, they reported 5 deaths in 84 TAPVR patients without heterotaxy and 7 deaths in 38 patients with TAPVR and heterotaxy. However, this mortality difference was not statistically significant. They noted a 9.8% reoperation rate after TAPVR repair, but 58% of the reoperations for pulmonary vein stenosis were in heterotaxy patients compared with nonheterotaxy patients. Foerster and colleagues [12] reported a higher 47% restenosis rate after TAPVR repair in heterotaxy patients. Only one patient in our cohort of heterotaxy syndrome, PA/PS, and TAPVR, has required reintervention for pulmonary vein stenosis. Morales and colleagues [6] found no statistically significant difference in survival between TAPVR in heterotaxy and nonheterotaxy patients but did report PA and the need for systemic-to-pulmonary shunt to be risk factors for death among their entire cohort.

Three patients in our series underwent two-ventricle repairs. These patients were initially palliated with a systemic-to-pulmonary artery shunt, and then a Rastelli pathway was used to connect the morphologic left ventricle to the aorta. At this time, right ventricle to pulmonary artery continuity was established using a Contegra conduit in all 3 patients.

Stent angioplasty of the ductus arteriosus can be performed for ductal-dependent pulmonary or systemic circulation. When we use ductal stents for neonates with heterotaxy and ductal-dependent pulmonary circulation, our institutional policy is to use a stent 4 mm or lesser in diameter, due to concern for diastolic runoff physiology leading to systemic malperfusion and necrotizing enterocolitis. For ducts larger than 4 mm in diameter, prostaglandins are stopped a few hours before ductal stenting to allow the use of an appropriately sized stent for the patient’s body weight. We have avoided ductal stenting for tortuous ducts (with curvature greater than 180 degrees).

Ductal stenting is performed using a prograde approach (femoral venous access), retrograde approach (femoral arterial access), or by carotid artery cutdown approach. Immediately after ductal stenting, an intravenous heparin drip is started and aspirin is given for 48 hours. Anticoagulation is continued with low-molecular-weight heparin and aspirin.

At the time of discharge, these patients are enrolled in our Safe-at-Home program for interstage monitoring of single-ventricle patients. Close monitoring of saturations and serial echocardiograms is done to evaluate for ductal stent obstruction due to thrombosis or in-stent restenosis. At our institution, ductal stents are typically evaluated in the catheterization laboratory 3 to 4 months after implantation.

We are encouraged by the early results obtained with less traditional methods, such as primary ductal stenting or the use of bilateral autologous systemic-to-pulmonary artery shunts, that allow for avoiding on-cardiopulmonary bypass systemic-to-pulmonary artery shunting with or without neonatal pulmonary artery unifocalization. Heterotaxy is often associated with multiple intracardiac lesions, and when subgroups of cardiac lesions or interventions are examined within the study
group, the subanalyses is often underpowered. This is an inherent limitation of our study. For example, we cannot make statistically significant inferences about the subgroup where ductal stenting was attempted.

In patients with discontinuous pulmonary arteries that are not amenable to ductal stenting, our preferred technique of reconstruction has been with the subclavian artery and carotid artery with a “turn down” flap that connects it to the ipsilateral discontinuous pulmonary artery in the form of a “classic shunt” (Figures 6 and 7). We perform this technique without cardiopulmonary bypass, and it has allowed us the versatility to treat the discontinuous pulmonary arteries in heterotaxy with its positional anomalies such as dextrocardia or right aortic arch (Figures 8 and 9). This technique has also allowed us the maximal use of autologous vascular tissue for centralization of pulmonary arteries at a later stage.

We have performed bidirectional Glenn on both of the patients that underwent a classic shunt for discontinuous pulmonary arteries and no significant distal vascular ischemia has occurred with the use of these autologous tissue shunts. A third patient with discontinuous pulmonary arteries underwent bilateral ductal stents and delayed centralization of the pulmonary arteries. The remaining 2 patients with bilaterally discontinuous pulmonary arteries underwent neonatal centralization of the pulmonary arteries, and the patient that underwent simultaneous TAPVR repair died. Currently, we use primary ductal stenting as our preferred treatment modality for stabilization of pulmonary blood flow in patients with heterotaxy, pulmonary atresia, and TAPVR with or without discontinuous pulmonary arteries.

Thirteen patients in our entire cohort had associated TAPVR. We believe that careful selection of TAPVR patients for nonsurgical intervention in the neonatal period is possible and likely beneficial. In our institution, every neonatal patient with heterotaxy and PA/PS with TAPVR is assessed carefully according to the appearance of the pulmonary veins on echocardiography or in the catheterization laboratory, chest radiographic findings, and clinical examination. We use a combination of all these factors to decide on the need for neonatal surgical intervention for TAPVR in heterotaxy and PA/PS. For example, an acyanotic TAPVR patient with PA, a large patent ductus arteriosus, clear chest roentgenogram, and stable hemodynamics would not be treated with neonatal TAPVR repair in our institution. We have speculated that moderate or more sonographic flow acceleration in the pulmonary venous pathway should be expected in this patient with excessive pulmonary blood flow and, if all other clinical indicators are favorable, that this is a patient who does not require urgent primary TAPVR repair. Jonas and colleagues [13] have also recommended selective TAPVR surgical intervention in patients with heterotaxy syndrome.

The mortality rate for neonatal TAPVR repair in single-ventricle heterotaxy patients with PA tends to be very high. We have observed that this death can often be
the result of associated morbid propensities in these patients, such as postoperative arrhythmias, significant common atrioventricular valve regurgitation, and marginal single-ventricle performance after a lengthy TAPVR repair, pulmonary artery unifocalization, or a systemic-to-pulmonary artery shunt placement with resultant volume overload. We have, therefore, used echocardiographic, catheterization, radiographic criteria, and clinical presentation to carefully define the group that requires neonatal TAPVR repair.

Heterotaxy patients also have associated noncardiac malformations, including intestinal malrotation, that can cause significant morbidity and death. Surgical management of malrotation with the Ladd procedure can also be associated with significant cardiac morbidity and death. So we prefer to perform the Ladd procedure on these patients after the second-stage palliation with bidirectional Glenn. We only recommend an earlier Ladd procedure for patients who have clinical evidence of obstruction with bilious vomiting before the second-stage palliation [14].

In conclusion, this series represents our recent experience of heterotaxy patients with associated PA or PS. This remains a challenging and very heterogeneous group. The presence of TAPVR remains a risk factor for death in heterotaxy patients with PA or PS.

We are continuing to modify and refine our techniques for the management of these patients. We are encouraged by the early results obtained with less traditional methods, such as ductal stenting or classic bilateral systemic-to-pulmonary artery shunts, that allow for creation or stabilization of pulmonary blood flow without the use of cardiopulmonary bypass. We believe that careful selection of TAPVR patients for delayed pulmonary vein repair beyond the neonatal period is also possible and likely beneficial. We are sufficiently encouraged to maintain this as our current strategy.

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References