Pulmonary Atresia/Intact Ventricular Septum: Influence of Coronary Anatomy on Single-Ventricle Outcome

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Background. We investigated the influence of coronary artery abnormalities on outcome in patients with pulmonary atresia/intact ventricular septum (PA-IVS) for planned single-ventricle palliation.

Methods. Catheterization and medical records were reviewed in patients with PA-IVS for planned single-ventricle palliation at our institution between 2000 and 2012. Primary outcome was death or transplantation. Patients with confirmed or strong suspicion of stenosis in 2 or more main coronary arteries or coronary ostial atresia were defined as having right ventricle–dependent coronary circulation (RVDCC); those with stenosis of 1 main vessel or normal anatomy were defined as having non-RVDCC.

Results. Of 58 patients with PA-IVS, 17 (30%) underwent single-ventricle palliation. Ten (59%) had RVDCC (3 with ostial atresia) and 7 (41%) had non-RVDCC. Median follow-up time was 8.2 years (0 months–11.3 years), with 1 patient in each group lost to follow-up. Five patients with RVDCC died, including the 3 patients with ostial atresia, and 1 underwent transplantation at 6 months of life. No deaths occurred after second-stage palliation. Three of the 4 surviving patients with RVDCC completed a Fontan operation, and 2 of these patients had evidence of cardiac ischemia on follow-up. No deaths occurred among patients with non-RVDCC. Kaplan-Meier analysis demonstrated significantly better survival in patients with non-RVDCC (100%) than in patients with RVDCC (40%) (p = 0.026).

Conclusions. In patients with PA-IVS undergoing single-ventricle palliation, RVDCC is associated with high early mortality, especially with coronary ostial atresia. There should be early consideration of transplantation in neonates with RVDCC. Patients with non-RVDCC undergoing single-ventricle palliation have excellent long-term outcomes, with no mortality seen in this series.


Pulmonary atresia/intact ventricular septum (PA-IVS) is a rare congenital cardiac malformation characterized by a broad morphologic spectrum with varying degrees of tricuspid valve (TV) and right ventricular (RV) hypoplasia. A variety of coronary artery abnormalities are common in this lesion [1], with RV-to-coronary artery fistulas occurring in 31% to 61% of patients [2–7]. RV- dependent coronary circulation (RVDCC) is defined as dependence of myocardial perfusion on fistulous connections from the RV caused by significant proximal coronary artery obstruction and inadequate antegrade flow through the coronary arteries. RVDCC is present in 9% to 34% of patients with PA-IVS [5, 6, 8–10].

Because of the heterogeneous nature of this lesion and its associated coronary anomalies, clinical management can prove to be complicated, and despite management strategies—ranging from biventricular repair by right ventricular decompression to single-ventricle palliation or cardiac transplantation, or both—overall mortality for patients with PA-IVS ranges from 19% to 42% [3, 5, 6, 11]. Single-ventricle palliation is often pursued when the size of the TV and RV is prohibitive of biventricular physiology or in the presence of RVDCC and accounts for most of the mortality in patients with PA-IVS [9, 12–15]. The purpose of this single-center study is to assess short- and long-term outcomes of single-ventricle palliation for patients with PA-IVS and to evaluate the contribution of coronary artery anatomy and the presence of RVDCC on survival.
Patients and Methods

Data Collection

After approval of the Columbia University Medical Center Institutional Review Board, surgical and catheterization laboratory clinical databases were queried to identify patients with the diagnosis of PA-IVS admitted to our hospital between January 2000 and December 2012. Medical records, echocardiograms, angiograms, and operative reports were reviewed. In all patients, the diagnosis of PA-IVS was made by transthoracic echocardiography, and cardiac catheterization with angiography was then performed to assess coronary artery anatomy and suitability for 2-ventricle repair. The decision to pursue single-ventricle palliation was at the discretion of the medical team and was based on clinical factors that included but were not limited to adequacy of the TV, RV, and pulmonary valve and the presence of significant coronary artery abnormalities. Patients in whom coronary artery anatomy was not delineated by angiography before surgical intervention or those who underwent biventricular repair were excluded from the study population.

Echocardiography reports from the time of initial postnatal diagnosis were reviewed to obtain measurements of the TV annulus diameter (expressed as a z score corrected for patient body surface area) and the degree of right ventricular hypoplasia (as qualitatively described by the reviewing echocardiographer).

Each patient underwent a right ventricular angiogram at the time of cardiac catheterization to assess for the presence of ventriculocoronary connections and right ventricular size. In patients with ventriculocoronary connections, an aortic angiogram was obtained and, when necessary, selective coronary injections were performed to determine coronary artery anatomy and the presence of coronary stenosis or atresia, or both. Based on initial angiography, patients were identified as having RV-dependent coronary circulation (RVDCC) or non-RVDCC. RVDCC was defined as confirmed or strong suspicion of stenosis in 2 or more main coronary arteries (defined as the left main, left anterior descending, circumflex, and right main coronary arteries) or any presence of coronary ostial atresia (Fig 1). Those with stenosis of only 1 main vessel or normal coronary anatomy were classified as non-RVDCC. If available, follow-up coronary angiographic findings for survivors were compared with the first angiogram to evaluate the evolution of the coronary anatomy over time. All angiograms were reviewed again by a single interventional pediatric cardiologist (AJT) for the purpose of this study.

Primary outcome was defined as death or heart transplantation. Patient and procedural variables assessed for association with primary outcome included birth weight, TV size, and age at first surgical intervention. Loss to follow-up was defined as the lack of any record for 6 months after initial hospitalization or 3 years after a second surgical palliation, or both.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 21.0 (SPSS Inc, Chicago, IL). The data are presented as mean ± standard deviation or median and range as appropriate. Survival estimates were obtained by means of the Kaplan-Meier method. Two-tailed t-test analysis was used to analyze normally distributed continuous variables.

Results

Study Population

During the study period, 58 patients were admitted with the diagnosis of PA-IVS. Two patients did not undergo cardiac catheterization and 39 of 56 patients (70%) underwent interventions resulting in biventricular physiology. After excluding these patients, a total of 17 patients (30%) were considered for single-ventricle palliation and constituted the study population. Table 1 summarizes the characteristics of the study population. The mean birth weight of the study population was 3.0 ± 0.45 kg, and all patients were born at greater than 36 weeks of gestational age. The diagnosis was made prenatally in 14 patients (78%). TV annulus measurements on initial echocardiograms were available for 13 of the 17 patients,
with a median TV z score of –3.83 (range, –2.21 to –5.2). Severe right ventricular hypoplasia was diagnosed in 14 patients, and moderate hypoplasia was seen in 3 patients. Of the 17 patients eligible for single-ventricle palliation, 14 underwent Blalock-Taussig (BT) shunt placement (3 died before any surgical intervention), with the median age at placement of the BT shunt of 6 days (range, 3–16 days).

Ventriculocoronary connections were present in 15 of 17 (88%) patients with PA/IVS in the single-ventricle palliation group and in 8 of 39 (20%) of those who underwent biventricular repair. In the single-ventricle palliation groups, 10 (59%) patients were diagnosed with RVDCC and 7 (41%) with non-RVDCC. Thus, the incidence of RVDCC in our total population was 18% (10 of 56). The coronary artery anatomy of the 10 patients with RVDCC is detailed in Table 2. Of the patients with non-RVDCC, 5 had normal coronary anatomy (right-dominant coronary artery system in 4 patients) and 2 had single stenosis in the right coronary artery (both with left-dominant coronary artery systems).

There were 2 patients (1 in each group) for whom no follow-up information was available after the first operation, making our follow-up rate 88%. Median follow-up time for the entire cohort was 8.2 years (range, 0 months–11.3 years).

### Primary Outcome

Overall, 5 patients died and 1 underwent heart transplantation because of ischemia (6 of 17 [35.3%]). All deaths and the heart transplantation occurred in the group with RVDCC. Therefore, the primary outcome was reached in 60% of patients with RVDCC and 0% in the patients with non-RVDCC. Kaplan-Meier analysis (Fig 2) demonstrated significantly better transplant-free survival in patients with non-RVDCC versus patients with RVDCC ($p = 0.026$). The 5 deaths of patients with RVDCC and the 1 transplantation all occurred within the first 6 months of life. Death occurred before discharge from first hospitalization in 4 of the 5 mortalities, including the 3 patients with coronary ostial atresia who died before any surgical intervention.

### Causes of Mortality

Of the 4 intrahospital mortalities, 1 patient with coronary ostial atresia died just after cardiac catheterization because of cardiac ischemia and severe dysfunction. The second patient with a stenotic single left coronary artery and an atretic right coronary artery confirmed by autopsy had care withdrawn on the seventh day of life after the parents decided against cardiac transplantation. The third patient with left coronary artery atresia underwent cardiac catheterization at 2 days of age and within 3 days ischemia developed and there were electrocardiographic changes with rising troponin levels and lactic acidosis;

### Table 1. Characteristics of Patients With Pulmonary Atresia/Intact Ventricular Septum Undergoing Single-Ventricle Palliation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>17</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 8, Female 9</td>
</tr>
<tr>
<td>Birth weight</td>
<td>3 ± 0.45 kg</td>
</tr>
<tr>
<td>Age at BTS operation</td>
<td>6 d (range, 2–16 d)</td>
</tr>
<tr>
<td>RVDCC</td>
<td>Yes 10 (58.8%), No 7 (41.2%)</td>
</tr>
<tr>
<td>TV z score (n = 12)</td>
<td>&gt; −2.5 1 (8.3%), −2.5 to −3.5 2 (16.7%), &lt; −3.5 9 (75%)</td>
</tr>
</tbody>
</table>

BTS = Blalock-Taussig shunt; RVDCC = right ventricle-dependent coronary circulation; TV = tricuspid valve.

### Table 2. Coronary Artery Anatomy of Patients With RVDCC

<table>
<thead>
<tr>
<th>Patient</th>
<th>Deceased/Transplantation</th>
<th>Single Coronary Article</th>
<th>LCA</th>
<th>RCA</th>
<th>LAD</th>
<th>Cx</th>
<th>Dominance</th>
<th>Confirmed (C) or Suspicious (S)</th>
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<tr>
<td>1</td>
<td>Yes</td>
<td>No</td>
<td>Atresia</td>
<td>Stenosis</td>
<td>Stenosis</td>
<td>. .</td>
<td>L</td>
<td>C</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Atresia</td>
<td>Stenosis</td>
<td>Stenosis</td>
<td>U</td>
<td>C</td>
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</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Atresia</td>
<td>Stenosis</td>
<td>. .</td>
<td>. .</td>
<td>U</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>No</td>
<td>Severe stenosis</td>
<td>Stenosis</td>
<td>Stenosis</td>
<td>U</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>No</td>
<td>. .</td>
<td>Severe stenosis</td>
<td>Stenosis</td>
<td>. .</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>. .</td>
<td>Stenosis</td>
<td>Stenosis</td>
<td>. .</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>7*</td>
<td>NA</td>
<td>No</td>
<td>. .</td>
<td>Stenosis</td>
<td>Stenosis</td>
<td>Stenosis</td>
<td>R</td>
<td>C</td>
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<td>Stenosis</td>
<td>Stenosis</td>
<td>. .</td>
<td>C</td>
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<tr>
<td>9</td>
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<td>No</td>
<td>. .</td>
<td>Stenosis</td>
<td>Stenosis</td>
<td>Stenosis</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
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<td>No</td>
<td>No</td>
<td>. .</td>
<td>Stenosis</td>
<td>Stenosis</td>
<td>. .</td>
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</table>

*Cx = Circumflex artery; LAD = left anterior descending artery; LCA = left coronary artery; RCA = right coronary artery; RVDCC = right ventricle-dependent coronary circulation; U = undetermined.*
this patient died of severe cardiac dysfunction. The fourth early death was in a patient who had received a BT shunt at 16 days of age after cardiac catheterization revealed severely stenotic left and right coronary arteries. This patient had significant cardiac ischemia and dysfunction and died of multisystem organ failure at 41 days of age. The autopsy of this patient demonstrated acute subendocardial ischemia and multiple infarcts of varying ages. The only death to occur after discharge from the initial hospitalization and placement of a BT shunt was a patient who died suddenly at home at 6 months of age, with the subsequent autopsy revealing a patent BT shunt and stenotic lesions in the right coronary artery and left anterior descending artery with signs of ischemia. One patient received a heart transplant during the interstage 1 period at 4 months of age. After discharge from a BT shunt operation, she was listed for transplantation at 3 months of age after presenting with irritability and signs of ischemia on electrocardiography. Pathologic examination of the explanted heart showed evidence of chronic ischemia with irregular intimal and medial proliferation in several intramyocardial branches (Fig 3).

**Long-Term Outcomes**

No deaths occurred after second-stage palliation, with 3 of the 4 surviving patients with RVDCC having undergone Fontan completion, 1 with a fenestrated lateral tunnel and 2 with extracardiac tunnels. Two of the 3 patients who underwent Fontan procedures demonstrated signs of cardiac ischemia on review of their follow-up information. One patient had evidence of ischemia and infarction by positron emission tomography in the distribution of the left anterior descending coronary artery just before his Fontan operation. The second patient had ischemic cardiac arrest during diagnostic catheterization before his bidirectional Glenn (BDG) operation but went on to Fontan completion several years later. None of these patients showed progression of coronary artery disease on follow-up angiography. The 3 surviving patients with RVDCC who underwent Fontan procedures had normal left ventricular systolic function on echocardiography and no significant arrhythmias at most recent follow-up.

No deaths or ischemic events occurred among patients with non-RVDCC (n = 7), with 1 patient lost to follow-up. Median follow-up time for the patients with non-RVDCC was 8.4 years (range, 3.7–10.4 years). Five patients have
undergone completion of Fontan palliation, 4 with fenestrated lateral tunnels and 1 with a nonfenestrated extracardiac tunnel. One patient is awaiting a Fontan procedure after having undergone a BDG operation (Fig 3). Available echocardiographic follow-up of 5 of the 7 patients with non-RVDCC demonstrate qualitatively normal left ventricular function. Two of the patients with non-RVDCC have significant atrial arrhythmias, both with atrial fibrillation/flutter on medications, 1 complicated by sinus slowing, necessitating the placement of an atrial pacemaker.

There was no statistical association between birth weight, TV size, and age at first surgical intervention and outcome.

Follow-Up Angiography
Follow-up coronary artery angiography was repeated between 2 and 5 years of age in the 3 patients with RVDCC and in 4 of 5 of the patients with non-RVDCC who had ventriculocoronary connections on initial angiography. Two patients with RVDCC had no changes in the extent of ventriculocoronary connections or coronary artery stenosis, and the third patient with RVDCC had a larger circumflex artery and overall fewer ventriculocoronary connections. Among the 4 patients with non-RVDCC, 3 had a significant decrease in the number of ventriculocoronary connections. Of the patients with right coronary artery stenosis, 1 had no change in the degree of stenosis and the second patient was lost to follow-up.

Comment
The incidence of PA-IVS is estimated at 4 to 8 per 100,000 live births, composing approximately 1% to 3% of all congenital cardiac disease [5, 6, 16–18]. Although the specific cause of this lesion is unknown, a proposed mechanism is an abnormality in right ventricular blood flow after ventricular septation is completed, resulting in right ventricular outflow tract obstruction and leading to the associated abnormalities commonly found with PA-IVS—varying degrees of RV hypoplasia and hypertrophy, TV abnormalities, and ventriculocoronary connections. Because of the lack of egress from the RV, right ventricular hypertension may be responsible for the persistence of embryologic ventricular coronary sinusoids. It is proposed that high pressure and turbulent flow within these connections from the RV to the coronary arteries may cause endothelial injury and myointimal hyperplasia, resulting in coronary artery stenoses, atresia, or interruptions. Delineating the presence of ventriculocoronary connections and RVDCC through cardiac catheterization is an imperative first step in the algorithm of management strategies for patients with PA-IVS.

The incidence of RVDCC was 18% in our study, similar to other series in which it has been reported in 9% to 34% of patients with PA-IVS [5, 6, 8–10]. Mixed data exist regarding the contribution of RVDCC to the overall outcome of patients with PA-IVS. Coles and colleagues [3], in a large single-institution sample, recognized early on that the presence of RV-coronary artery connections and RVDCC were risk factors for postoperative death in neonates with PA-IVS, with stenosis or interruption of the proximal left anterior descending coronary artery a uniformly lethal anomaly. In the 1993 Congenital Heart Surgeons Society report on outcomes of neonates with PA-IVS, RVDCC was also found in multivariate analysis to be a significant risk factor for mortality [5]. Their follow-up report in 2004, however, stated that aberrations in coronary arteries were not a significant risk factor for death [6]. A multicenter study in the United Kingdom and Ireland also did not find, in their multivariate analysis, that the presence of RVDCC to be a risk factor for poor outcome in 183 patients with PA-IVS [11]. These studies have been inconsistent in finding the presence of RVDCC to be a significant risk factor for mortality, which may be caused by the subjectivity with which RVDCC is judged.

Our results demonstrate overall mortality of patients undergoing single-ventricle palliation for PA-IVS to be similar to that in other series at 35.3%. However, all 6 deaths occurred in patients with identified RVDCC, resulting in 60% mortality for this cohort. As in other studies [9, 12], we found that mortality from likely cardiac ischemia occurs early after a BT shunt operation and that those who survive to the second-stage palliation procedure have good long-term outcomes. Five of the deceased patients presented with clinical evidence of acute ischemia. The sixth patient, who died suddenly at home after an episode of irritability, had evidence of acute and chronic myocardial ischemia at autopsy. Newborns and early infants with signs of ongoing myocardial ischemia should be considered for heart transplantation because these patients can deteriorate rapidly. Although our mortality rate is based on a small sample of patients and should not be extrapolated to the entire RVDCC population, it reveals the small number of appropriate predictors for outcome in RVDCC. As in other studies [4, 12], coronary ostial atresia was associated with 100% mortality. However, there were no other differences in the extent of coronary anomalies between patients who survived and those who did not. Delineation of coronary artery anatomy by angiography is difficult in these patients because of the presence of abnormal small vessels, unusual arborization, and ventriculocoronary connections. Although angiography is the gold standard to determine coronary artery anatomy, it is not an indicator of ischemia. Therefore, patients with advanced coronary artery disease may be relatively free of ischemia and vice versa.

One concerning finding in our series that has not been addressed in previous studies was the evidence of myocardial ischemia in 2 of our 3 surviving patients with PA-IVS and RVDCC who underwent Fontan procedures. Despite normal left ventricular systolic function at their most recent cardiac follow-up, 1 patient had evidence of ischemic changes on a myocardial perfusion scan in the distribution of the left anterior descending artery before Fontan completion, and a second patient had ischemic electrocardiographic changes and cardiac arrest during a diagnostic cardiac catheterization. Follow-up...
angiography in the RVDCC group showed no progression of coronary disease in any of the patients. However, progression of coronary artery disease was reported in a couple of patients in a previous study with a larger cohort of patients [12]. The lack of progression of coronary artery disease in most patients, at least in the short term, suggests that the endothelial injury attributed to the high-pressure turbulent flow transmitted from the RV to the coronary arteries may have its most deleterious effect during vessel development in fetal life. Because systemic hypertension is a well-known risk factor for coronary artery disease in the adult population, patients with RVDCC may carry a higher risk of the development of worsening coronary artery disease in early adulthood. In concordance with other series [12], we noted a decrease in the number of ventriculocoronary connections in 1 patient with RVDCC and in 3 of 4 patients with non-RVDCC on follow-up angiography. The clinical implication of this finding is unclear and may be related to varying intraventricular pressure over time. There should be continued vigilance for ischemia in patients with PA-IVS with RVDCC who undergo single-ventricle palliation because they may still be at risk for progression of coronary artery disease or silent myocardial ischemia despite preserved overall systolic function.

Survival was 100% among patients who surpassed the BDG operation; all had normal systolic left ventricular function by echocardiography, no documented significant arrhythmias, and no other significant comorbidities on last follow-up. Past series investigating the outcomes of the Fontan operation in patients with PA-IVS also demonstrated encouraging outcomes, with survival exceeding 80% to 92% [14, 15]. Despite satisfactory survival, longer term morbidities have been described. In 1 series of adult patients with PA-IVS in which 12 of 20 patients had single-ventricle palliation, there were 3 deaths at a median age of 32 years, 1 of which was secondary to “cardiac arrest” after Fontan revision [19]. This adult series also found that patients with PA-IVS after the Fontan operation had a higher incidence of atrial arrhythmias compared with those having undergone biventricular repair. In addition, repeated interventions were common, including Fontan revisions, Maze procedures, and mitral valve repair or replacement. Further long-term follow-up of patients with PA-IVS with single-ventricle physiology is necessary to more accurately prognosticate the long-term outcome of these patients.

The main limitations of this study relate to its retrospective nature. The small number of patients with multiple risk factors limits the predictive power of this analysis. As a single-institution study, our patient number was limited and may not be representative of all patients with PA-IVS and patients with PA-IVS and RVDCC. However, mortality in all our patients was clearly associated with ischemia, which underscores the relationship between significant coronary artery disease and poor outcome.

The presence of RVDCC in patients with PA-IVS undergoing single-ventricle palliation is associated with higher mortality rates during the first 6 months of life. Patients with coronary ostial atresia and those presenting with acute myocardial ischemia in the neonatal period had 100% mortality in our study and should be urgently evaluated for heart transplantation. Because neonates with PA-IVS and RVDCC are at high risk for latent ischemia, particular care in optimizing myocardial oxygen supply and demand determinants by avoiding anemia, tachycardia, hypotension, and fever is recommended. There should also be a low threshold for mechanical support for infants showing signs of ischemic progression. Although no deaths occurred beyond second-stage palliation, diagnostic testing to rule out silent ischemia should be performed in long-term survivors.

References