Outcomes in Patients with Alagille Syndrome and Complex Pulmonary Artery Disease

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Objective To assess outcomes in a large cohort of patients with Alagille syndrome (ALGS) who underwent pulmonary artery reconstruction surgery for complex pulmonary artery disease.

Study design Patients with ALGS who underwent pulmonary artery reconstruction surgery at Lucile Packard Children's Hospital Stanford were reviewed. Patients were examined as an overall cohort and based on the primary cardiovascular diagnosis: severe isolated branch pulmonary artery stenosis, tetralogy of Fallot (TOF) without major aortopulmonary collateral arteries (MAPCAs), or TOF with MAPCAs.

Results Fifty-one patients with ALGS underwent pulmonary artery surgery at our center, including 22 with severe branch pulmonary artery stenosis, 9 with TOF without MAPCAs, and 20 with TOF and MAPCAs. Forty-one patients (80%) achieved a complete repair. Five of the patients with TOF with MAPCAs (25%) underwent complete repair at the first surgery, compared with 8 (89%) with TOF without MAPCAs and 19 (86%) with isolated branch pulmonary artery stenosis. At a median follow-up of 1.7 years after the first surgery, 39 patients (76%) were alive, 36 with a complete repair and a median pulmonary artery:aortic systolic pressure of 0.38. Nine patients (18%), including 8 with isolated branch pulmonary artery stenosis, underwent liver transplantation.

Conclusions Most patients with ALGS and complex pulmonary artery disease can undergo complete repair with low postoperative right ventricular pressure. Patients with TOF/MAPCAs had the worst outcomes, with higher mortality and more frequent pulmonary artery interventions compared with patients with TOF without MAPCAs or isolated branch pulmonary artery stenosis. Complex pulmonary artery disease is not a contraindication to liver transplantation in patients with ALGS. *(J Pediatr 2021;229:86-94)*.

Alagille syndrome (ALGS) is a complex, multisystem disorder that frequently involves the pulmonary arteries.[1-3] Pulmonary vascular anomalies can range from mild peripheral pulmonary artery stenosis to tetralogy of Fallot (TOF) with pulmonary atresia and major aortopulmonary collateral arteries (MAPCAs), with isolated branch pulmonary artery stenosis/hypoplasia the most common finding.[4-6] The strategic goal in these conditions is to treat the pulmonary artery anomalies with a combination of surgical techniques out to the segmental level, in order to achieve the lowest possible right ventricular (RV) pressure.[7-10] Although patients with ALGS are a minority of those undergoing pulmonary artery reconstruction, they present unique challenges given the complex and variable nature of pulmonary vascular supply and additional comorbidities, such as liver disease.[8,11-15]

Methods

Pediatric patients (age <18 years) diagnosed with ALGS by standard criteria[16] who underwent surgery for pulmonary artery reconstruction at Lucile Packard Children's Hospital Stanford (LPCHS) between June 2004 and April 2020 were identified. In addition to examining the overall cohort, patients were grouped by primary diagnosis: isolated branch pulmonary artery stenosis without intracardiac anomalies, TOF without MAPCAs, and TOF with MAPCAs. We excluded patients with ALGS who underwent surgery for other conditions (eg, single ventricle defects). This project was approved by the Stanford University Institutional Review Board.

ALGS	Alagille syndrome
LPCHS	Lucile Packard Children's Hospital Stanford
MAPCAs	Major aortopulmonary collateral arteries
RV	Right ventricular
TOF	Tetralogy of Fallot

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Demographic and clinical data were extracted from the medical record. Early mortality was defined as death during the postoperative hospitalization or within 30 days of surgery. Follow-up was conducted by medical record review.

The surgical and anesthetic techniques that we use in patients undergoing pulmonary artery reconstruction have been detailed previously.[8-14,17,18] Our approach emphasizes early single-stage complete repair, including intracardiac repair if applicable and full pulmonary artery reconstruction consisting of unifocalization in patients with MAPCAs and pulmonary artery augmentation of all affected central, lobar, and segmental branches. Unifocalization and pulmonary artery reconstruction were performed through a midline sternotomy, using a combination of techniques, including bifurcation ostioplasty and patch augmentation with a pulmonary homograft. Although catheter-based interventions were performed before referral in some patients, for severe multifocal pulmonary artery stenosis, we typically use transcatheter interventions only after surgical pulmonary artery reconstruction if indicated for residual or recurrent obstruction, and we do not place stents in these patients.

For this study, "complete repair" was defined as complete intracardiac septation along with full (bilateral if necessary) pulmonary artery reconstruction, including unifocalization in patients with MAPCAs, and pulmonary artery augmentation of all affected central, lobar, and segmental branches as indicated, or the procedure that was intended as "complete" surgical therapy in a given patient. Anything less than complete repair was defined as a palliative procedure. For example, in a patient with bilateral branch pulmonary artery stenosis, single-stage bilateral pulmonary artery reconstruction was considered a complete repair, but disconnection of one pulmonary artery branch to rehabilitate with a shunt would be considered palliative. In general, after a palliative procedure, the pulmonary artery circulation is evaluated in 3-6 months, with the aim of completing the repair at a subsequent surgery. Although pulmonary artery reconstruction in patients with isolated branch pulmonary artery stenosis is not typically discussed in these terms, the purpose of adopting the terms "complete repair" and "palliation" in this study was to allow for a comprehensive summary of patients with ALGS with different primary conditions and to indicate the intended therapeutic goal. Pulmonary artery interventions performed after complete repair were documented as surgical or transcatheter reinterventions.

Patients were defined as having severe liver disease if they had documented end-stage liver disease, portal hypertension (ascites, varices, splenomegaly), complications of chronic liver disease (variceal bleeding, spontaneous bacterial peritonitis), liver synthetic dysfunction, or cirrhosis or were listed for liver transplantation or underwent liver transplantation. Because the focus of this study was not on liver disease in ALGS, we did not obtain detailed information about liver-related outcomes after pulmonary artery surgery.

Data were presented descriptively as median (range) or number (%). Between-group comparisons were performed using the Wilcoxon rank-sum test or Fisher exact test. Competing outcome cumulative incidence curves were generated to depict the cumulative incidences of death, complete repair (with survival for at least 6 months after repair), and survival without complete repair. Analyses were performed using R version 3.6.1.

Results

The study cohort consisted of 51 patients with ALGS who underwent pulmonary artery surgery at LPCHS between June 2004 and April 2020 (**Table**). Underlying diagnoses included bilateral branch pulmonary artery stenosis in 22 patients (**Figure 1**), TOF without MAPCAs in 9 (**Figure 2**; available at www.jpeds.com), and TOF with MAPCAS in 20 (**Figure 3**; available at www.jpeds.com). One patient with ALGS with functional single-ventricle heart disease and MAPCAs was excluded. The median age at first LPCHS surgery was 1.6 years (range, 0-17.2 years); one-half (n = 25) of the population had undergone surgical or transcatheter pulmonary artery interventions before referral, and 33% (n = 17) had multiple previous interventions, which are detailed below. Before the first LPCHS surgery, RV pressure was suprasystemic in 14 patients (27%), systemic in 20 (39%), 75%-95% systemic in 11 (22%), and <75% systemic in 6 (12%) (**Table**). Patient flow and outcomes are depicted in **Figure 4**.

Sixteen patients (31%) had severe liver disease, including 12 with isolated branch pulmonary artery stenosis, 1 with TOF without MAPCAs, and 3 with TOF and MAPCAs. Nine of these patients (18% of the entire cohort) underwent liver transplantation, 2 at other institutions before referral, 6 at our center following pulmonary artery reconstruction surgery (5 after complete repair and 1 after palliation but before complete repair), and 1 at the referring institution after pulmonary artery reconstruction surgery.

Among the 22 patients with isolated branch pulmonary artery stenosis (**Figure 1**), the pulmonary artery stenosis was bilateral in 20 and unilateral in 2. Eleven patients (50%) had pulmonary artery interventions before referral (**Table**); 10 patients had undergone catheter interventions (branch pulmonary artery angioplasty with stenting in 5, pulmonary artery angioplasty with no stents placed in 4, pulmonary valvuloplasty in 1, and other in 1) and 5 had undergone surgical interventions (pulmonary artery augmentation in 4 and ascending aortic and coarctation repair in 1). RV pressure was systemic or higher in 6 patients (27%), 75%-95% of systemic pressure in 10 (46%), and elevated but <75% of systemic in 6 (27%).

During the first LPCHS surgery, 19 of the 22 patients with isolated pulmonary artery stenosis underwent repair, and 3 were palliated with unilateral pulmonary artery reconstruction, followed by completion of the repair with 1 additional surgery on a separate admission. On predischarge lung perfusion scintigraphy after repair (n = 18), most patients had balanced flow, as summarized in the **Table**, but 7 (32%) had ≥60% flow to 1 lung and 2 (9%) had ≥70% flow to 1 lung.

During a median follow-up of 1.5 years (range, 0-15.4 years), there were 2 deaths, including 1 from unrelated head trauma. The other patient who died had undergone multiple previous cardiac surgeries, and in addition to right pulmonary artery reconstruction, the surgery at LPCHS included augmentation coronary arterioplasty and revision of a previous supravalvular aortic repair. The patient died 50 days after repair due to cardiac arrest from respiratory failure.

No patients in this group underwent pulmonary artery reintervention after repair. At a median follow-up of 1.5 years (range, 0-15.4 years), the median pulmonary artery:aortic systolic pressure was 0.34, and only 1 patient had a ratio >0.5 (**Table**). An example of the reconstructed pulmonary artery circulation is shown in **Figure 5** (available at www.jpeds.com). One patient was prescribed anti-pulmonary hypertensive therapy at the most recent follow-up.

Table. Demographic, diagnostic data, and outcomes after complete repair in patients with ALGS overall and according to diagnostic group

Variables	All patients (N = 51)	Branch pulmonary artery stenosis (N = 22)	TOF without MAPCAs (N = 9)	TOF with MAPCAs (N = 20)
Demographic/historical				
Female sex, n (%)	16 (31)	8 (36)	3 (33)	5 (25)
Previous cardiac intervention, n (%)	25 (49)	11 (50)	7 (78)	7 (35)
Catheter intervention, n (%)	19 (37)	10 (45)	6 (67)	3 (15)
Surgery, n (%)	17 (33)	5 (23)	6 (67)	6 (30)
Multiple previous interventions, n (%)*	17 (33)	7 (32)	6 (67)	4 (20)
Age at first LPCHS surgery, y, median (range)	1.6 (0.0-17.2)	3.2 (0.9-13.8)	1.5 (0.0-3.9)	0.4 (0.0-17.2)
Baseline hemodynamics				
Mean RA pressure, mmHg, median (range)	7 (1-14)	7 (3-14)	7 (6-13)	7 (1-8)
RV systolic pressure, mmHg, median (range)	80 (43-175)	75 (43-140)	93 (63-145)	85 (62-175)
RV:aortic systolic pressure ratio, median (range)	1.0 (0.4-2.1)	0.8 (0.4-1.6)	1.1 (0.8-1.8)	1.0 (1.0-2.1)
Suprasystemic, n (%)	14 (27)	3 (14)	5 (56)	6 (30)
Systemic, n (%)	20 (39)	3 (14)	3 (33)	14 (70)
75%-95% of systemic, n (%)	11 (22)	10 (45)	1 (11)	0 (0)
<75% of systemic, n (%)	6 (12)	6 (27)	0 (0)	0 (0)
Severe liver disease, n (%)	16 (31)	12 (55)	1 (11)	3 (15)
Liver transplantation, n (%)	9 (18)	8 (36)	1 (11)	0 (0)
Before first LPCHS surgery, n (%)	2 (4)	2 (9)	0 (0)	0 (0)
After first LPCHS surgery, n (%)†	7 (14)	6 (23)	1 (11)	0 (0)
Type of first LPCHS surgery				
Complete repair, n (%)	32 (63)	19 (86)	8 (89)	5 (25)
With unifocalization, n (%)	5 (10)	0 (0)	0 (0)	5 (25)
Without unifocalization, n (%)	27 (53)	19 (86)	8 (89)	0 (0)
Palliation, n (%)	19 (37)	3 (14)	1 (11)	15 (75)
Achieved complete repair, n (%)	41 (80)	22 (100)	8 (89)	11 (55)
Age at repair, y, median (range)	2.3 (0.0-17.2)	3.9 (0.9-13.8)	1.6 (0.0-3.9)	0.7 (0.2-17.2)
As first LPCHS surgery, n (%)	32 (63)	19 (86)	8 (89)	5 (25)
After previous palliation at LPCHS, n (%)	9 (18)	3 (14)	0 (0)	6 (30)
Years from palliation to repair, median (range)	0.7 (0.4-2.5)	0.7 (0.5-2.0)	—	0.6 (0.4-2.5)
Early outcomes after repair, median (range)				
Pulmonary artery systolic pressure‡, mmHg (n = 34)	33 (18-48)	29 (18-45)	33 (28-42)	37 (22-48)
Pulmonary artery:aortic systolic pressure ratio	0.36 (0.20-0.53)	0.31 (0.20-0.53)	0.35 (0.27-0.49)	0.41 (0.24-0.46)
Lung perfusion scan (n = 33), median (range)				
Right lung, % of total	60 (40-81)	58 (44-81)	61 (52-64)	61 (40-75)
Left lung, % of total	40 (19-60)	42 (19-56)	39 (36-48)	39 (25-60)
Early mortality, n (%)	3 (6)	1 (5)	1 (11)	1 (5)
Follow-up after complete repair				
Duration of follow-up, y, median (range)	2.0 (0.0-15.4)	1.5 (0.0-15.4)	1.6 (0.0-8.4)	7.9 (0.1-13.2)
Mean RA pressure, mmHg (n = 21), median (range)	7 (3-13)	5 (3-12)	7 (5-9)	8 (3-13)
Pulmonary artery systolic pressure‡, mmHg (n = 25), median (range)	37 (21-95)	34 (25-42)	39 (28-95)	42 (21-84)
Pulmonary artery:aortic systolic pressure ratio, median (range)	0.38 (0.22-0.73)	0.34 (0.22-0.60)	0.35 (0.28-0.42)	0.40 (0.25-0.73)
Pulmonary artery:aortic pressure ratio >0.5, n (%)	3 (7)	1 (5)	0 (0)	2 (17)
Follow-up status overall, n (%)				
Deceased	12 (24)	2 (9)	2 (22)	8 (40)
Alive	39 (76)	20 (91)	7 (78)	12 (60)
Alive with complete repair	36 (71)	20 (91)	7 (78)	9 (45)
Alive with palliation	3 (6)			3 (15)
Prescribed PH medication	5 (10)	1 (5)	0 (0)	4 (20)

RA, right atrium; *PH*, pulmonary hypertension.
*Had more than 1 total pulmonary artery catheter or pulmonary artery surgical intervention.
†All but 1 of these patients underwent liver transplantation after complete repair.
‡Pulmonary artery pressures reflect the central (main) pulmonary artery.

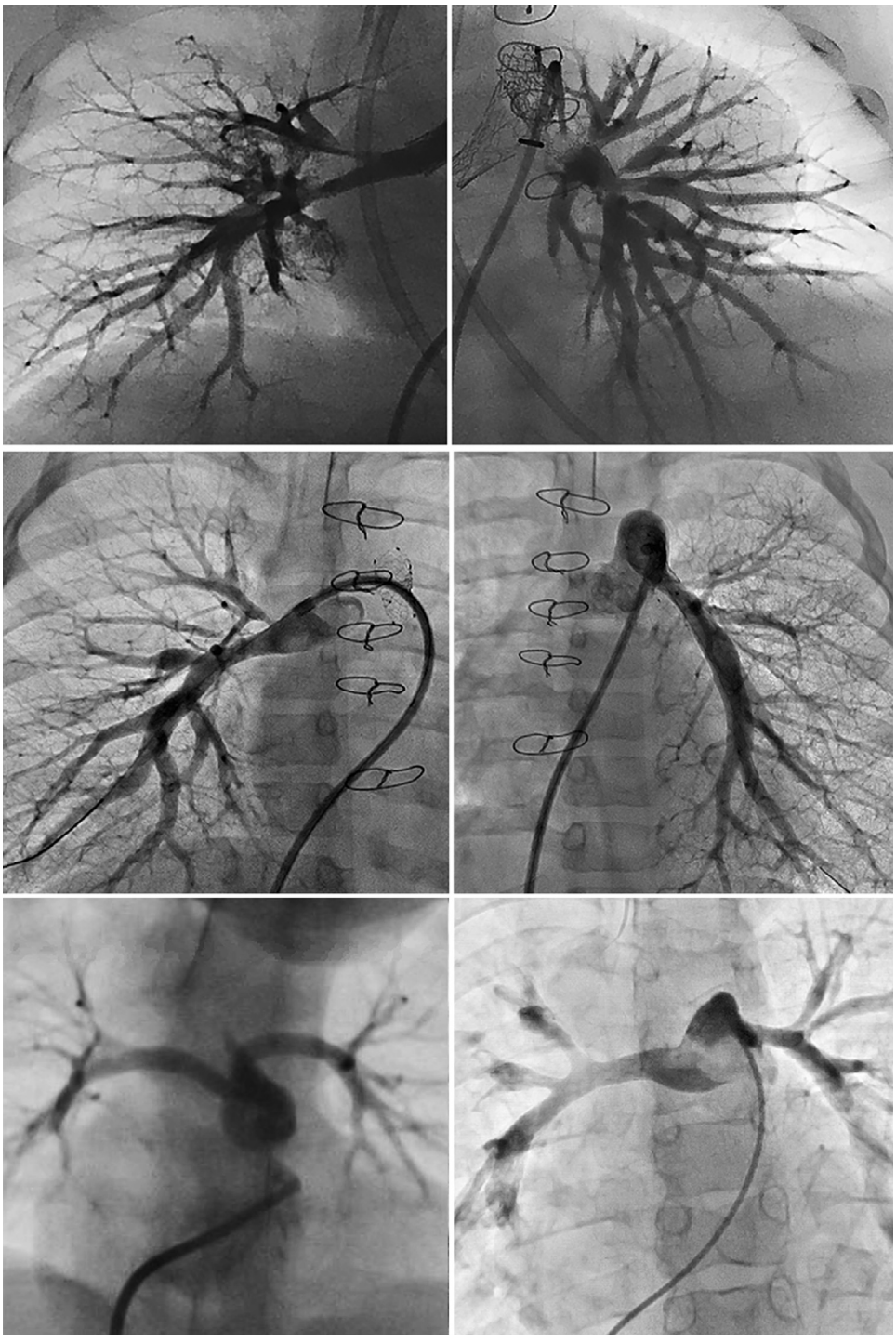

Figure 1. Angiograms depicting the anatomy of the pulmonary circulation in 4 patients with ALGS and bilateral branch pulmonary artery stenosis and normal intracardiac anatomy before the first surgery at our institution. The top and middle rows depict left and right pulmonary artery images for 2 patients who had surgery and pulmonary artery stents placed before referral. The images in the bottom row show the anatomy of the pulmonary artery system in 2 other patients who did not undergo intervention before referral. The images illustrate the variable hypoplasia, stenosis, and arborization of the pulmonary arteries.

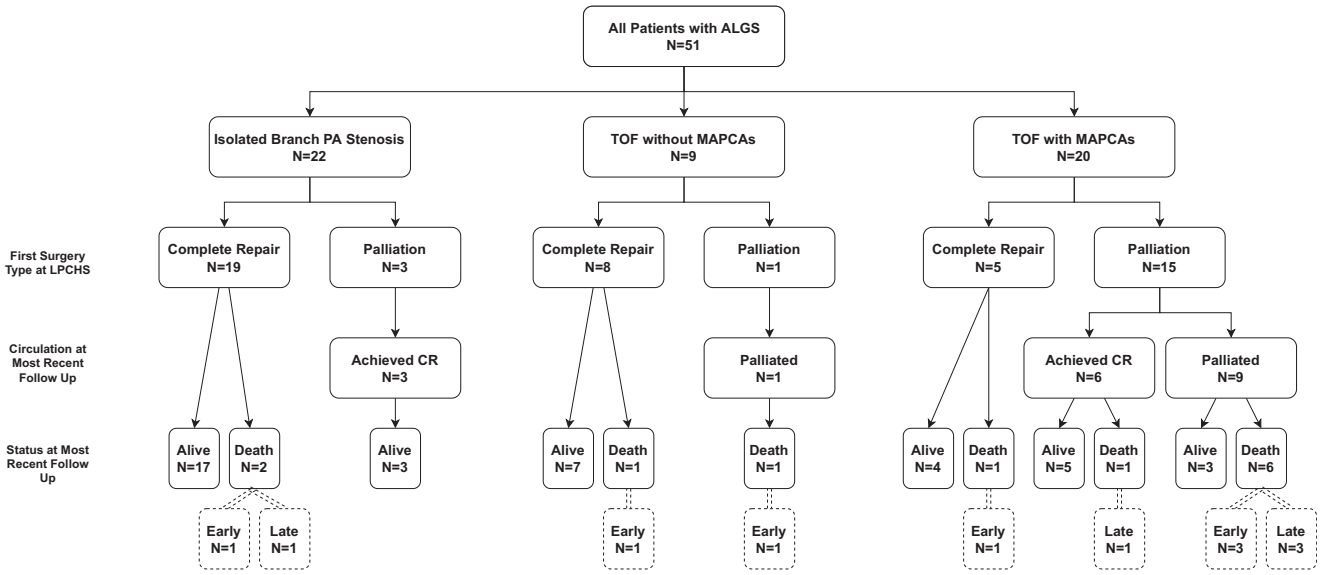

Figure 4. This flow diagram depicts the flow of patients according to type of surgery and survival after surgery at our center.

Twelve of the 16 patients with severe liver disease (75%) had isolated pulmonary artery stenosis, including both of the deaths described above. Of the 10 surviving patients with isolated branch pulmonary artery stenosis and severe liver disease, 8 underwent liver transplantation, 2 before referral and 6 after repair.

Of the 9 patients with TOF without MAPCAs (**Figure 2**), 7 (78%) had undergone cardiovascular surgery (n = 6; TOF repair in 4, pulmonary artery augmentation in 1, and shunt placement only in 1) and/or transcatheter intervention (n = 6; branch pulmonary artery angioplasty with stenting in 4, pulmonary artery angioplasty alone in 1, RV outflow tract stenting in 2, and pulmonary valvuloplasty in 2) before referral (**Table**). RV pressure was systemic or suprasystemic in all but 1 patient.

Eight of these 9 patients (89%) achieved a complete repair during the first LPCHS surgery, and 1 patient underwent palliation consisting of pulmonary artery reconstruction with a systemic-to-pulmonary artery shunt. The palliated patient had a complicated postoperative course and died of multisystem failure 73 days postoperatively. Of the 5 repaired patients who underwent lung perfusion scintigraphy before discharge, 3 were unbalanced with ≥60% flow to 1 lung (**Table**).

One of the 8 patients who underwent a complete repair during the first LPCHS surgery died in the early postoperative period after pulmonary artery revision and takedown of the repair to a shunted circulation. Three others underwent surgical pulmonary artery revision: 1 at a different institution 2.8 years after the first surgery, 1 at our center 7.3 years later, and 1 at our center 1.3 years after the first surgery in preparation for liver transplantation the next day.

The 7 surviving patients with a complete repair were followed for a median of 1.7 years (range, 0-8.4 years) after the initial LPCHS surgery; the median pulmonary artery:aortic systolic pressure ratio was 0.35, and the ratio was <0.5 in all patients (**Table**). An example of postrepair pulmonary artery anatomy in a patient with TOF and no MAPCAs is shown in **Figure 6** (available at www.jpeds.com).

One patient with TOF without MAPCAs also had severe liver disease and underwent liver transplantation 2 years after the initial pulmonary artery reconstruction surgery.

Twenty patients had TOF with MAPCAs (**Figure 3**), 7 (35%) of whom had undergone cardiac intervention before referral (**Table**). Three patients had undergone catheter interventions (pulmonary artery angioplasty without stenting in 1, RV outflow tract stent placement in 1, and angioplasty/stenting of MAPCAs in 2), and 6 had undergone surgical interventions (TOF repair in 1, partial unifocalization and/or pulmonary artery augmentation in 3, and shunt placement only in 3). All 20 patients had systemic or suprasystemic RV pressure.

Five of these patients (25%) achieved complete repair at the initial LPCHS surgery, and the other 15 underwent palliation, either unifocalization/pulmonary artery reconstruction with a systemic-to-pulmonary artery shunt (or an RV-to-pulmonary artery conduit without ventricular septal defect closure in 1 case), or creation of an aortopulmonary window. There were 2 early deaths. One of these was a 17-year-old who had 4 pulmonary artery surgeries before referral and underwent complete repair during the first procedure at our center, which was complicated by persistent pulmonary hemorrhage. The other death was a newborn with profound cyanosis who underwent unifocalization without ventricular septal defect closure but died postoperatively from multiorgan failure.

The 18 early survivors, 14 of whom underwent palliation during the first LPCHS surgery, were followed for a median of 4.7 years (range, 0.2-13.2 years). Six of the palliated patients ultimately underwent complete repair, 3 of whom

had 5 intermediate procedures (3 surgical, 2 transcatheter), each before repair.

All 10 of the patients who survived complete repair, 4 as a first surgery at LPCHS and 6 after palliation, underwent postrepair surgical (n = 8) and/or transcatheter (n = 6) pulmonary artery reintervention, the first of which was a median of 8.7 months after repair (range, 3.5-57 months). One of these patients died 9.2 years postrepair from liver failure.

Five of the 8 palliated patients who did not achieve a complete repair died. Three of these patients survived to discharge but died 5.9-7.5 months after the first surgery and 2 died after surgical reintervention 3.2-3.4 years after the first surgery, including 1 who was reported previously[19] and 1 from pulmonary hemorrhage and cardiac arrest following bilateral unifocalization revision. Of the 3 surviving palliated patients, 1 was awaiting repair and 2 were unrepaired 4.8 years and 7.1 years later after undergoing multiple additional surgeries and interventional catheterizations.

At most recent follow-up, 12 of the 20 patients with TOF/MAPCAs were alive (60%), 10 with a complete repair. In 9 of those 10 patients, lung perfusion was unbalanced with ≥60% flow to 1 lung, but significant imbalance was uncommon, with ≥70% flow to 1 lung in only 2 patients. The median systolic pulmonary artery:aortic systolic pressure on follow-up evaluation was 0.40, and was >0.5 in 2 patients (**Table**). A central pulmonary artery angiogram obtained 8 years after the first LPCHS surgery is shown in **Figure 7** (available at www.jpeds.com) for a patient who underwent staged repair (3 operations) at our center after previous RV-pulmonary artery conduit placement and partial unifocalization elsewhere. At most recent follow-up at a median of 7.0 years after initial surgery, 3 of the 12 surviving patients were prescribed anti-pulmonary hypertensive medication.

Three patients with TOF/MAPCAs had severe liver disease, all of whom survived to discharge but died between 0.5 and 9.6 years later; all 3 were followed elsewhere, and additional records were not available. By correspondence, the primary cause of death in 1 patient was liver failure, although details were not available, including whether liver transplantation had been considered.

Overall, patients were followed for a median of 1.7 years after the first LPCHS surgery. Forty-one patients (80%) achieved a complete repair, 32 (63%) during the first surgery at LPCHS. In the 9 (18%) patients who underwent repair after a palliative first LPCHS surgery, 1-3 additional surgeries were performed to achieve repair at a median of 0.7 years later (range, 0.4-2.5 years). In the 33 patients who underwent predischarge lung perfusion scintigraphy after repair, significant imbalance (≥70% to 1 lung) was present in 4 patients. Thirteen of the 41 repaired patients underwent subsequent surgical (n = 11) and/or transcatheter (n = 8) pulmonary artery reinterventions, with the first reintervention a median of 9.5 months later (range, 3.5-57 months).

There were 12 (24%) deaths in the entire cohort, including 4 (8%) early after the first surgery and 2 (4%) after pulmonary artery reintervention surgery. Five of the deaths were in patients with severe liver disease, and none were in patients who had undergone liver transplantation; neither of these factors was significantly associated with mortality (P = .48 and .09, respectively). Among the 39 surviving patients, who were followed for a median of 2.7 years, 36 had a complete repair, and 3 had a palliated circulation. Five of the surviving patients were lost to follow-up. Estimated cumulative incidence functions for complete repair, death, and survival without complete repair are plotted in **Figure 8**. Five surviving patients (10%) were prescribed anti-pulmonary hypertensive medications. All patients who underwent liver transplantation (n = 9) were alive at the most recent follow-up at a median of 3.4 years (range, 0.1-15.4 years) after the first LPCHS surgery. There were no significant differences in achievement of complete repair or in the early postrepair or follow-up RV:aortic pressure ratios (in repaired patients) between patients with and without severe liver disease (P = .47, .91, and .65, respectively) or liver transplantation (P = .18, .81, and .58, respectively).

Discussion

In this study of 51 patients with ALGS who underwent surgery for severe pulmonary artery anomalies over a 16-year period, 80% achieved a complete repair with reasonable RV pressure and relatively balanced pulmonary blood flow. Outcomes were particularly good in patients with isolated branch pulmonary artery stenosis, with few deaths and pulmonary artery pressure less than one-half systemic in almost all cases. However, mortality in patients with ALGS following pulmonary artery reconstruction surgery remains high, particularly in those with TOF/MAPCAs. Compared with our overall population of patients with TOF/MAPCAs, in which 67% of patients underwent complete repair as the initial surgery at our center, patients with ALGS were more likely to have a palliative first operation, to die, and to undergo reintervention.[8]

These findings are consistent with previous observations regarding the complexity of management and outcomes in patients with TOF/MAPCAs and ALGS.[11,12] This may reflect the generally small intraparenchymal pulmonary artery and MAPCA branches and multiple stenoses, which can be difficult to quantitate, particularly because most patients had undergone previous interventions. Worse outcomes in patients with TOF/MAPCAs and ALGS also may reflect some degree of referral bias if patients with more severe or difficult anatomy were referred from elsewhere while those with more straightforward disease were treated locally. Although TOF is the most common intracardiac anomaly in patients with ALGS, it is far less common than isolated branch pulmonary artery stenosis, and among the subset of patients with ALGS with TOF in general, only a minority have MAPCAs.[5] Accordingly, our cohort might not be representative of patients with ALGS with important pulmonary artery disease.

All of the patients with TOF with MAPCAs who achieved complete repair underwent pulmonary artery reinterventions

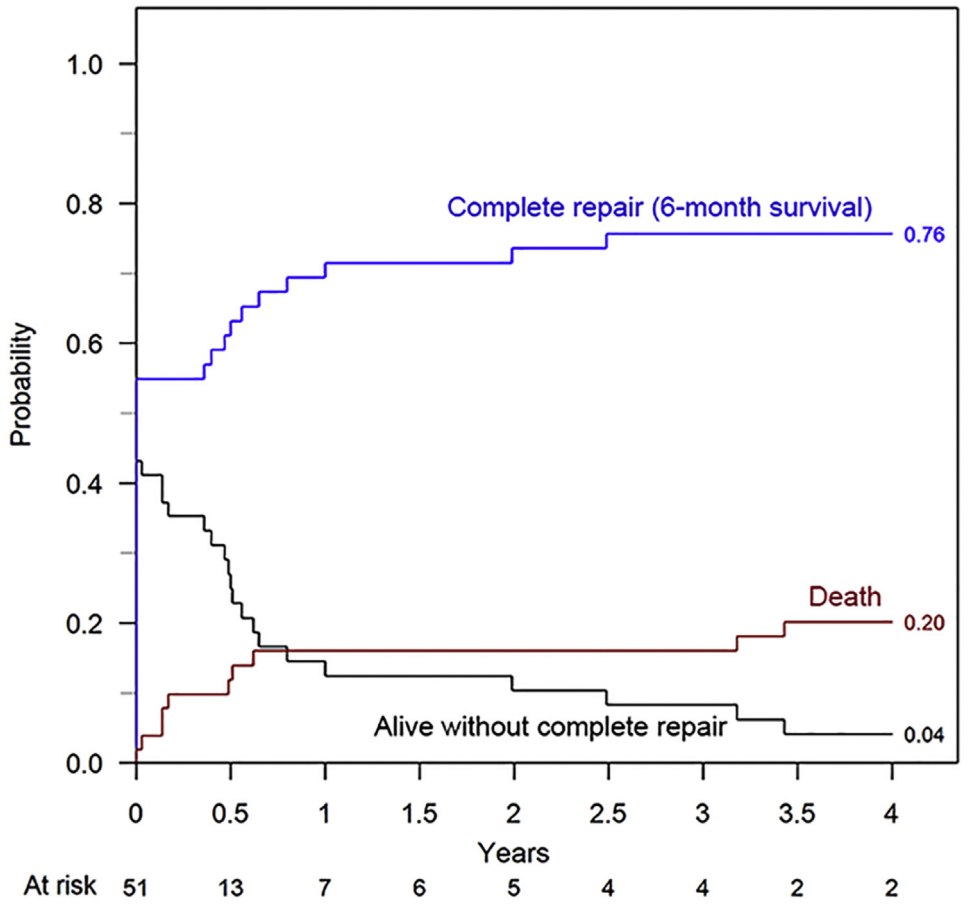

Figure 8. Competing outcomes plot depicting the estimated cumulative incidence functions for death, complete repair (with survival for at least 6 months), and survival without complete repair from the time of first surgery at our center among the entire ALGS cohort. The estimated cumulative incidence at 4 years is indicated at the right side of each curve.

after repair, and one-half of those who underwent staged repair had intermediate procedures between the first surgery and complete repair. Postrepair reinterventions are not a central aspect of our management strategy for TOF/MAPCAs in general, but are performed selectively depending on RV pressure and pulmonary flow distribution.[20,21] However, in this cohort of patients with ALGS with MAPCAs, all of those who survived after repair underwent pulmonary artery reintervention. Additional studies are needed to identify whether there are intrinsic differences between patients with ALGS with MAPCAs and those with other pulmonary artery anomalies. It is also unclear whether the high burden of pulmonary artery reintervention is true for all patients with ALGS and MAPCAs.

Patients with TOF without MAPCAs or with isolated branch pulmonary artery stenosis had better outcomes overall, were more likely to undergo complete repair at the first surgery, and were less likely to have pulmonary artery reintervention compared with those with MAPCAs. Survival in patients with isolated branch pulmonary artery stenosis was consistent with previous reports of pulmonary artery reconstruction surgery from our center.[17,22] It should be noted that the duration of follow-up was considerably longer for patients with MAPCAs than for those without MAPCAs, so comparisons between groups may be confounded. Further evaluation is needed to determine whether long-term outcomes in patients with ALGS differ according to the type of underlying pulmonary artery disease.

In this study, 14 patients with severe liver disease were referred for pulmonary artery reconstruction, in most cases to improve candidacy for liver transplantation. Kamath et al reported cardiac disease (including pulmonary artery stenosis) in 40% of 58 patients with ALGS undergoing liver transplantation.[23] In that study, only 3 children had significant cardiac abnormalities, such as TOF, and details of cardiac or pulmonary artery interventions were not reported. Arnon et al, using the United Network of Organ Sharing database, reported higher mortality from cardiac complications in children with ALGS after liver transplantation than those who underwent transplantation for biliary atresia, but further insight into that association is precluded by the lack of detailed cardiac data in the database.[24] In our cohort, 8 of the 9 patients who underwent liver transplantation had isolated branch pulmonary artery stenosis, and all were alive a median of 3.4 years after the first pulmonary artery reconstruction surgery. Five patients with severe liver disease who

did not undergo liver transplantation died; 2 with isolated branch pulmonary artery stenosis died from complications unrelated to liver disease and 3 with TOF/MAPCAs died after pulmonary artery reconstruction surgery, 1 from liver failure at a referring institution and 2 from unknown causes within 6 months of pulmonary artery surgery.

The few previous reports of liver transplantation after treatment of pulmonary artery disease describe relatively straightforward pulmonary artery anomalies compared with our cohort,[25,26] but support our experience that pulmonary artery disease alone is not a contraindication to liver transplantation in patients with ALGS and end-stage liver disease. Given the prolonged surgical and bypass times required for pulmonary artery reconstruction surgery with expected hepatic sequelae, all patients with ALGS and significant liver disease undergo evaluation by a transplantation hepatologist and transplantation surgeon before pulmonary artery reconstruction surgery at our center. Postoperatively, the hepatology team consults daily in the intensive care unit to monitor for signs of liver dysfunction.

This investigation was subject to the limitations of a retrospective study. Most patients received ongoing care at the referring institution, and it is possible that important details were not captured in our database. Some patients were lost to follow-up to our center, which may bias our findings. For this study, we decided not to compare the AGLS cohort with patients with similar pulmonary artery disease, because we have described these cohorts previously.[8,11,12,17,22] Although the concept of "complete repair" is not typically applied to patients with isolated branch pulmonary artery stenosis without intracardiac disease, we felt that it was useful to consider all patients in this heterogeneous cohort with common terminology to reflect achievement of the most complete surgical therapy possible.

Most patients with ALGS and severe pulmonary artery disease can undergo repair with low RV pressure. Although the overall procedure burden was relatively high, and reinterventions were often necessary, most patients had a good outcome, with 90% of patients who survived a complete repair alive at a median of 7.9 years after the first LPCHS surgery. This study also showed that patients with severe liver disease can undergo complex pulmonary artery repair, and that those with repaired pulmonary artery anomalies can undergo successful liver transplantation. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

50 Years Ago Today: The Expanding Phenotype of Larsen Syndrome

Latta RJ, Graham CB, Aase J, Scham SM, Smith DW. Larsen's Syndrome: A Skeletal Dysplasia with Multiple Joint Dislocations and Unusual Facies. J Pediatr 1971;78:291-8.

Fifty years ago, Latta et al reported a 6-month-old male infant with multiple joint dislocations including the knee, hip, and elbow joints, as well as bilateral clubfoot deformities. The child had mid facial flattening and a low nasal bridge. Skeletal radiographs were significant for shortening of the proximal fibula; bilateral heel valgus with forefoot varus; shortening of the metatarsals, metacarpals, and phalanges; and hypoplasia of the distal half of the humerus. Spinal radiographs were significant for flattened hypoplastic vertebrae. The patient's radiographic features were very similar to those reported among 6 children, representing sporadic occurrences in their families, 21 years prior in *The Journal* by Larsen et al.[1] Inheritance for Larsen syndrome was postulated to be autosomal dominant or autosomal recessive. Other features associated with Larsen syndrome include short stature, hypertelorism, flattened nasal bridge, cleft palate, hearing loss, and accessory carpal bones.

Monoallelic missense mutations in filamin B were subsequently identified in 5 families with affected individuals affected by Larsen syndrome.[2] Filamins are cytoplasmic localized proteins that stabilize actin filament networks through their linkage to the cellular membrane and forming a platform for cell signaling to take place.

Larsen syndrome is a clinically and genetically heterogeneous syndrome. Homozygous or compound heterozygous mutations in *CHST3* have been associated with autosomal recessive Larsen syndrome, which is characterized by multiple joint dislocations in the neonatal period and evolves into spondyloepiphyseal dysplasia Omani type associated with kyphoscoliosis, disc degeneration, arthritis involving the spine hand hips, and dysplastic heart valves. Additional autosomal recessive forms of Larsen syndrome are characterized by mutations in *B4GALT7*and *GZF1*, which encodes GDNF-inducible zinc finger protein 1, a transcription factor with unknown function.[3] *GZF1*-mediated Larsen syndrome is associated with severe myopia and milder skeletal involvement.

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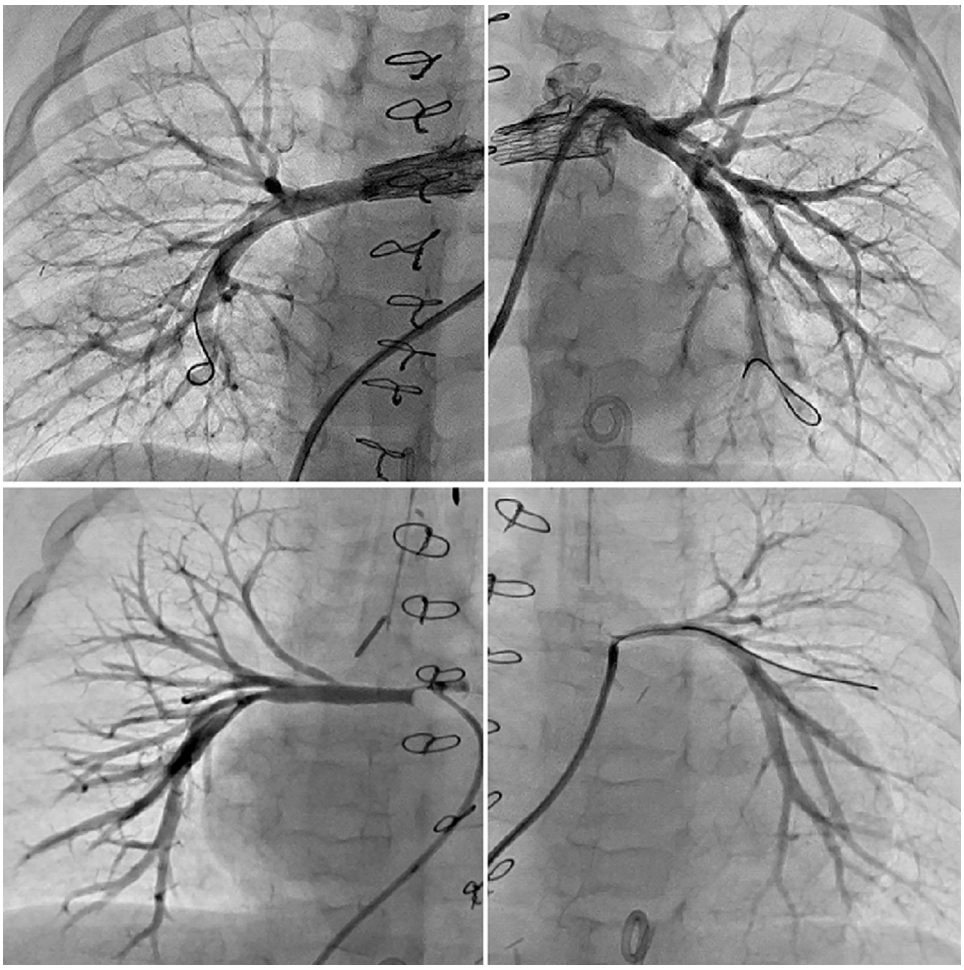

Figure 2. Angiograms depicting the anatomy of the pulmonary circulation in 2 patients with ALGS and TOF without MAPCAs before the first surgery at our institution. Both patients had undergone surgery before referral, and the top patient had pulmonary artery stents placed previously. Each row depicts the right and left pulmonary artery in the same patient.

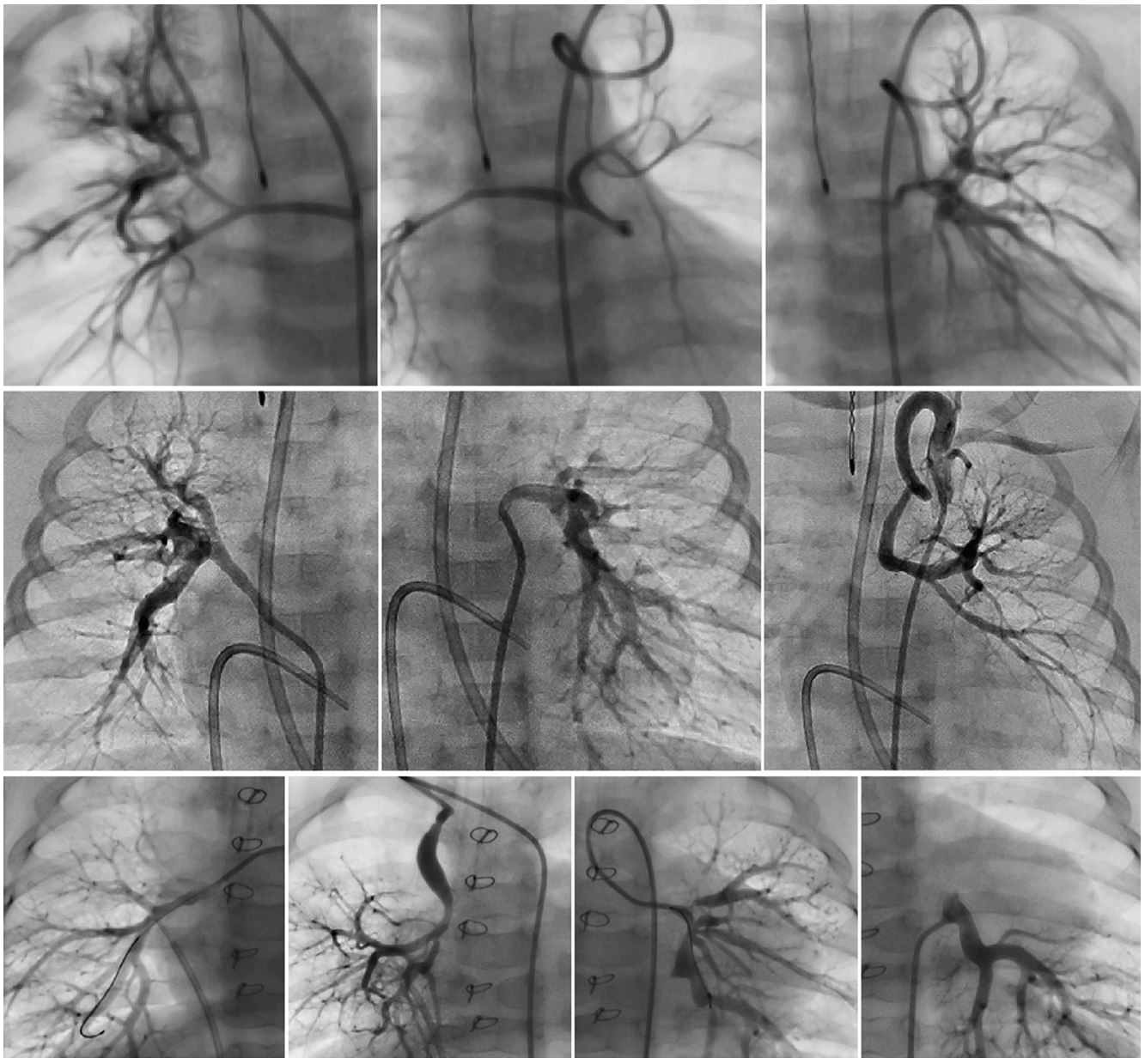

Figure 3. Angiograms depicting the anatomy of the pulmonary circulation in 3 patients with ALGS and TOF/MAPCAs before the first surgery at our institution. Each row depicts images for a single patient. The bottom patient had undergone surgery before referral, but the top 2 had not. The images illustrate the variable hypoplasia, stenosis, and arborization of native pulmonary arteries and MAPCAs.

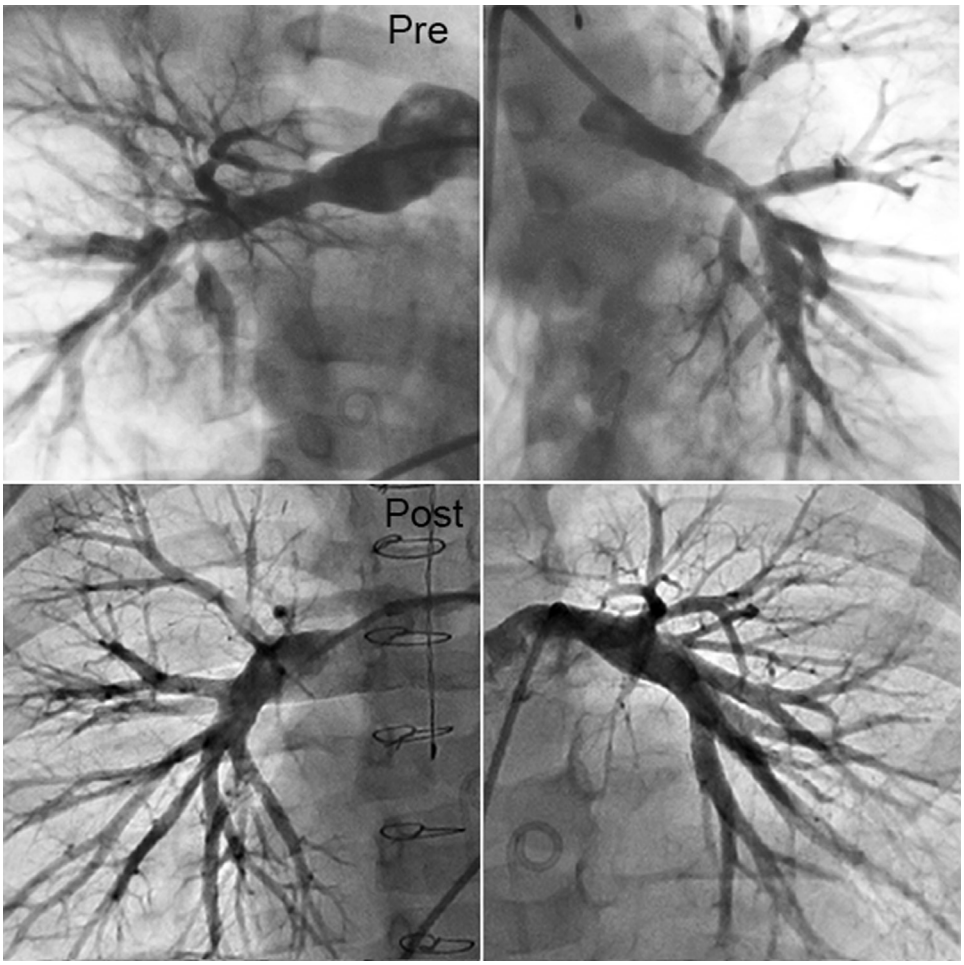

Figure 5. Series of angiograms demonstrating the pulmonary artery anatomy in a patient with isolated branch pulmonary artery stenosis before (pre) and after (post) surgery at our center. The preoperative images (top) show multilevel stenosis and hypoplasia in both the right (left panels) and left (right panels) branch pulmonary arteries, which were substantially improved and almost normal in appearance after repair (bottom).

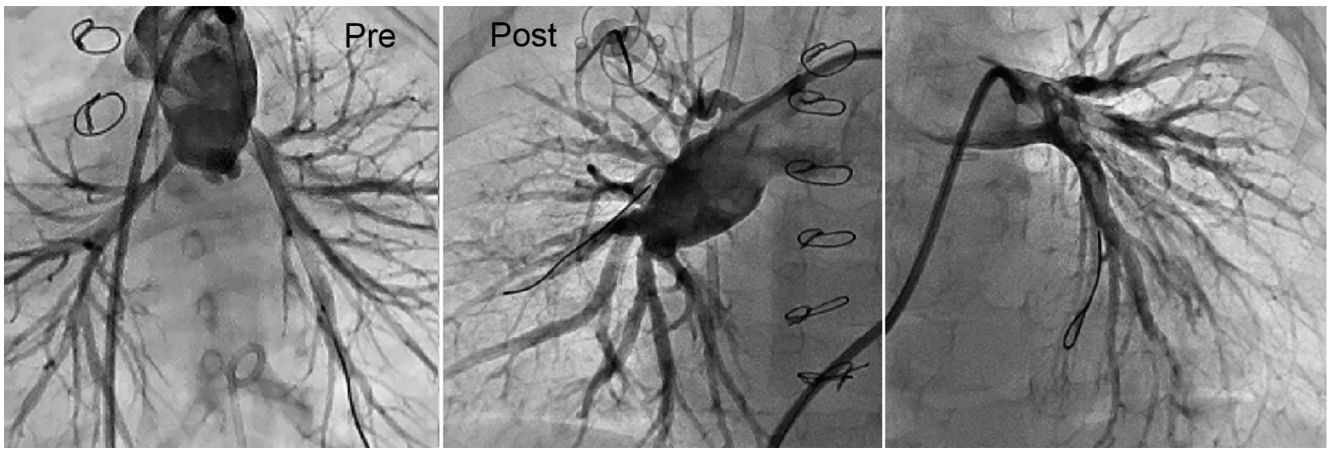

Figure 6. Angiographic images in a patient with TOF and no MAPCAs who underwent repair with an RV-pulmonary artery conduit and ventricular septal defect closure before referral demonstrating diffusely small branch pulmonary arteries and modest distal stenoses (pre), with larger central and distal branches after repair at our center (post).

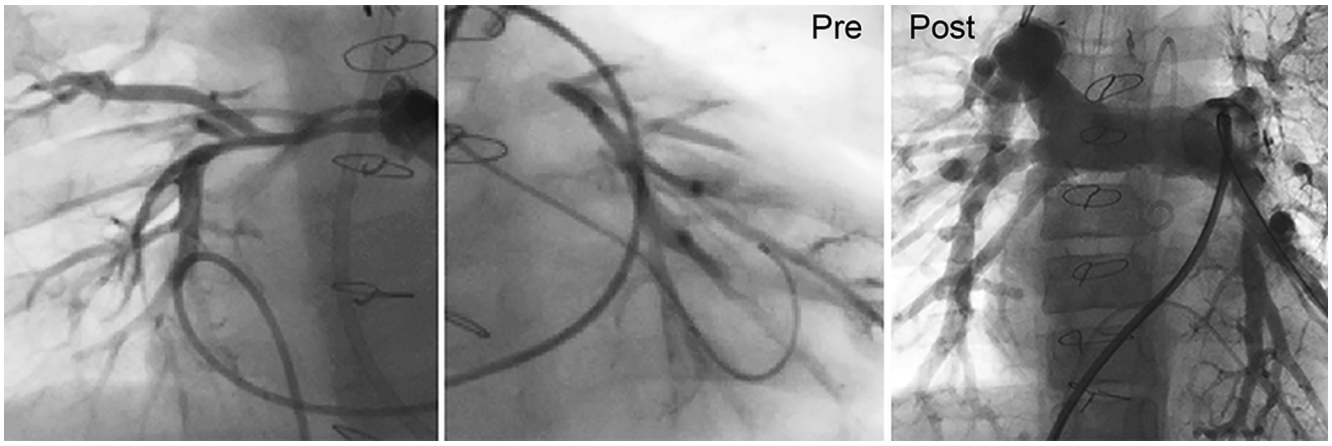

Figure 7. Series of angiograms in patient with TOF/MAPCAs who underwent partial unifocalization to an RV-pulmonary artery conduit before referral showing the partially unifocalized MAPCAs (left) and the atretic left pulmonary artery (middle) imaged on catheterization before the first surgery at our center (pre). Complete repair was performed during the third operation at our center, and the postrepair angiogram shown in the right panel demonstrates the reconstructed pulmonary artery system 8 years after the first LPCHS surgery (post).