Programmatic Approach to Management of Tetralogy of Fallot With Major Aortopulmonary Collateral Arteries

A 15-Year Experience With 458 Patients

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Background—Tetralogy of Fallot with major aortopulmonary collateral arteries is a complex and heterogeneous condition. Our institutional approach to this lesion emphasizes early complete repair with the incorporation of all lung segments and extensive lobar and segmental pulmonary artery reconstruction.

Methods and Results—We reviewed all patients who underwent surgical intervention for tetralogy of Fallot and major aortopulmonary collateral arteries at Lucile Packard Children's Hospital Stanford (LPCHS) since November 2001. A total of 458 patients underwent surgery, 291 (64%) of whom underwent their initial procedure at LPCHS. Patients were followed for a median of 2.7 years (mean 4.3 years) after the first LPCHS surgery, with an estimated survival of 85% at 5 years after first surgical intervention. Factors associated with worse survival included first LPCHS surgery type other than complete repair and Alagille syndrome. Of the overall cohort, 402 patients achieved complete unifocalization and repair, either as a single-stage procedure (n=186), after initial palliation at our center (n=74), or after surgery elsewhere followed by repair/revision at LPCHS (n=142). The median right ventricle:aortic pressure ratio after repair was 0.35. Estimated survival after repair was 92.5% at 10 years and was shorter in patients with chromosomal anomalies, older age, a greater number of collaterals unifocalized, and higher postrepair right ventricle pressure.

Conclusions—Using an approach that emphasizes early complete unifocalization and repair with incorporation of all pulmonary vascular supply, we have achieved excellent results in patients with both native and previously operated tetralogy of Fallot and major aortopulmonary collateral arteries. **(*Circ Cardiovasc Interv*. 2017;10:e004952. DOI: 10.1161/CIRCINTERVENTIONS.116.004952.)**

Key Words: Alagille syndrome ■ chromosome 22q11 ■ Digeorge syndrome ■ MAPCA ■ pulmonary artery ■ pulmonary atresia ■ TOF

Tetralogy of Fallot (TOF) with major aortopulmonary collateral arteries (MAPCAs) is a complex and heterogeneous disease with varying degrees of severity. While MAPCAs are present in 20% to 25% of patients with TOF and pulmonary atresia, the disease is rare and management varies considerably.[1,2] A number of investigators have described approaches to treatment for TOF with MAPCAs, but most series have been relatively small and results have been mixed.[3–15] Approaches prior to 1990 did not demonstrate a comprehensive strategy that logically addressed the variable morphology and physiology associated with this lesion. Beginning in 1992, our surgical group developed a complex management protocol aimed at addressing all of the morphological and physiological variants of this lesion optimally, with the goal of achieving complete repair in as many patients as possible, with pulmonary artery (PA) pressures as close to normal as possible. Important components of this approach include early surgical unifocalization independent of symptom status and incorporation of blood supply to all lung segments in the unifocalization process. The early experience with this approach was first described in 1995,[16] and an expanded cohort was reported in 2000.[17] Some groups have adopted this strategy,[3–7] while others continue to use approaches developed prior to 1992.[8–15] Subsequent, studies by our group and others have focused on the refinement of this strategy and outcomes in particular clinical subsets.

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WHAT IS KNOWN

- Tetralogy of Fallot with major aortopulmonary collateral arteries is a complex and heterogeneous congenital cardiovascular anomaly, which is managed with a variety of approaches.
- Incorporation of a greater number of lung segments into the pulmonary circulation and lower postrepair right ventricular pressure are associated with better survival in tetralogy of Fallot with pulmonary atresia.
- Using a strategy of complete unifocalization and repair with inclusion of all lung segments and extensive augmentation of the reconstructed pulmonary arterial circulation, the majority of patients can achieve complete repair in a single stage with low right ventricular pressure.

WHAT THE STUDY ADDS

- This study provides the most comprehensive assessment of outcomes in patients tetralogy of Fallot with major aortopulmonary collateral arteries managed according to a systematic institutional strategy of early complete unifocalization and repair.
- Early and intermediate survival is excellent among patients managed according to this approach, regardless of whether they underwent prior palliation elsewhere or had all procedures at our center.
- Patients undergoing complete single-stage unifocalization and repair had the best outcomes overall, including shorter length of stay, better survival, and lower postrepair right ventricular pressure.

However, an updated recent comprehensive overview of this experience has not been reported. In this study, we describe and analyze our 15-year surgical experience with TOF and MAPCAs at Lucile Packard Children's Hospital Stanford (LPCHS), during which time 458 patients were treated.

Methods

Patients

With approval from the Internal Review Board of Stanford University, we performed a retrospective review of all patients undergoing surgical intervention for MAPCAs at LPCHS from November 2001 to April 14, 2016. The present study included only patients with TOF and pulmonary valve atresia or near atresia, including both patients whose initial surgery was performed at LPCHS and those who underwent palliation or repair elsewhere and were subsequently referred to LPCHS for repair or revision (excluding simple conduit or pulmonary valve replacement). Patients whose first surgery was at LPCHS will sometimes be referred to as primary LPCHS patients. Patients were analyzed based on the initial surgical procedure and location of surgery (LPCHS or elsewhere). Early mortality was defined as death during the postoperative hospitalization or within 30 days of surgery if discharged before that time. Follow-up was conducted by a combination of medical record review and contact with the primary physician. If current information could not be obtained by those means, national death records (Social Security Death Index and the National Death Index) were reviewed.

Chromosomal anomalies were categorized as chromosome 22q11 deletion, Alagille syndrome (clinical or genetic diagnosis—assumed to be negative otherwise), or other chromosomal anomaly, which did not include patients with malformation syndromes but no documented genetic abnormality.

Anatomic Characterization

Echocardiography was used primarily to determine intracardiac anatomy. The anatomy of the pulmonary blood supply, including the presence of central PAs and the nature of MAPCA supply, was determined primarily by angiography or computed tomography. As discussed in the next section, computed tomography can be used as the primary imaging modality in a subset of cases in which it clearly demonstrates all MAPCAs to be dual supply, meaning that the central PAs arborize normally, with no lung segments receiving blood flow solely from a MAPCA without connection to the central PA system. However, if a potential PA to MAPCA connection cannot be defined adequately by computed tomography or the central PAs do not arborize normally, cardiac catheterization is performed for anatomic delineation and surgical planning. Traditional angiography remains our gold standard for anatomic delineation of MAPCAs and central PAs, and cardiac catheterization is always performed in cases of unclear distribution.

Surgical Strategy and Details

As initially described in 1995[16] and refined over time, our programmatic management algorithm aims for early complete unifocalization and intracardiac repair incorporating all lung segments, with augmentation of PA branches (whether native PAs or MAPCAs) down to the segmental level (Figure 1).[16] For the sake of clarity in this report, unifocalization refers to incorporation of MAPCAs and PAs into a single central PA system, along with augmentation or reconstruction of stenotic or hypoplastic branches, and complete repair refers to unifocalization, ventricular septal defect (VSD) closure, and placement of a conduit from the right ventricle (RV) to the unifocalized PAs. Single-stage complete repair refers to complete unifocalization and repair performed during a single procedure with no prior interventions.

Ideally, all patients undergo neonatal evaluation, with a primary goal of assessing clinical status and the anatomy of the pulmonary circulation. In addition to clinical status, anatomic characteristics that influence the initial management strategy, as diagrammed in Figure 1, include the number and distribution of MAPCAs, single or dual supply of each MAPCA, presence or absence and confluence of left and right native PAs, size and arborization pattern of the PAs (if present), and presence of a unilateral ductus arteriosus or anomalous PA from the ascending aorta (ie, hemitruncus).

The most critical aspect of the neonatal clinical evaluation is to estimate the overall pulmonary blood flow, which is reflected by the systemic oxygen saturation. Patients are categorized as having high, low, or balanced pulmonary blood flow (>90, <75%, or 75%–90%, respectively). If the saturation is 75% to 90%, which is the case in most newborns, there is no clinical need for neonatal intervention. However, the source of pulmonary blood supply must also be assessed to ascertain 2 variants that merit neonatal intervention: (1) a unilateral ductus arteriosus (or anomalous PA from the ascending aorta) with MAPCAs to the other lung, or (2) centrally confluent native PAs that arborize to all lung segments, such that all MAPCAs are dual supply. In the minority of neonates with a persistent systemic oxygen saturation either <75% or >90%, indicating high or low pulmonary blood flow, respectively, neonatal surgery is performed regardless of the anatomy of pulmonary blood supply. The operation performed in these patients depends on the clinical and anatomic details. If the native PAs are confluent and arborize to all lung segments (ie, all MAPCAs are dual supply), regardless of the systemic oxygen saturation, a surgical aortopulmonary (AP) window is created as a central shunt to promote growth of the native PA system. The patient then returns at ≈6 months of age for further assessment of PA growth. Because all lung segments are connected to the central PA system, unifocalization of MAPCAs is generally not necessary in these patients, although further PA

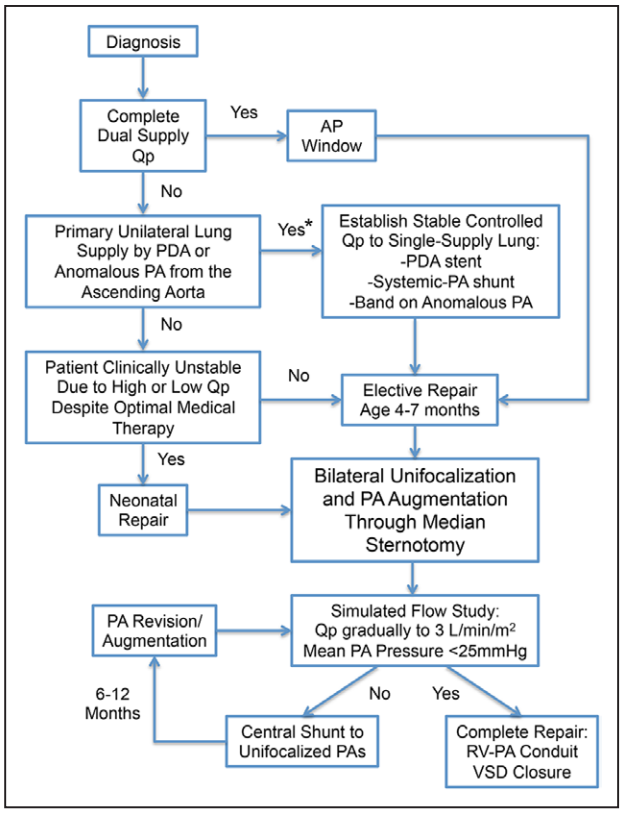

Figure 1. Usual treatment algorithm for newborns with tetralogy of Fallot and major aortopulmonary collateral arteries (MAPCAs). *Patients with a patent ductus arteriosus (PDA) or anomalous pulmonary artery (PA) from the ascending aorta (eg, hemitruncus) who have a small number of good-sized MAPCAs generally undergo neonatal repair instead of palliation to establish a stable controlled source of pulmonary blood flow (Qp). AP indicates aortopulmonary; RV, right ventricle; and VSD, ventricular septal defect.

augmentation/reconstruction is often required prior to intracardiac repair. If there is a unilateral ductus (either patent or closed) to one lung and MAPCAs to the other lung, regardless of the systemic oxygen saturation, a neonatal procedure is performed. Specifically, if the MAPCAs are favorable, single-stage complete repair is performed, but if the MAPCAs are unfavorable, the ductus is stented or a systemic-to-PA shunt is placed to the duct-dependent PA, and the patient is scheduled for unifocalization and assessment for intracardiac repair at 4 to 6 months of age. If the neonatal evaluation shows a systemic oxygen saturation >90% with failure to thrive, regardless of PA/MAPCA anatomy, complete repair is performed because the high pulmonary blood flow indicates that the pulmonary circulation is adequate to perform complete repair with low resistance. If the neonatal systemic oxygen saturation is <75%, neonatal unifocalization is performed regardless of the anatomy, either with or without simultaneous repair depending on the status of the MAPCAs.

Otherwise, patients are scheduled for surgery at 4 to 7 months of age, with a plan to perform complete unifocalization. At that procedure, either intracardiac repair will also be performed, making it a single-stage complete repair, or intracardiac repair will not be performed and a systemic-to-PA shunt will be placed. At the time of unifocalization, a decision is made about proceeding with intracardiac repair (ie, VSD closure and RV–PA conduit placement) on the basis of an intraoperative flow study, as described previously.[18] If the flow study demonstrates a high PA pressure (>25 mm Hg) at slightly supraphysiologic levels of flow, a shunt is placed from the aorta to the central PA, aiming for a mean PA pressure of 25 to 30 mm Hg, leaving the RV untouched. Fenestrated VSD closure is not performed. If the flow study demonstrates low PA pressure (≤25 mm Hg) at physiological levels of flow, intracardiac repair is performed. Rarely, other palliative procedures or variations may be performed, but for the purposes of this study, primary LPCHS patients were grouped into 3 categories based on the initial surgical intervention: single-stage complete repair (complete unifocalization and intracardiac repair at the initial procedure), AP window, and unifocalization to a shunt (also includes other palliative procedures).

While this strategy is followed for primary LPCHS patients, other approaches may have been used initially in patients referred after prior surgery elsewhere. Thus, for this study, patients treated before referral to LPCHS were grouped into 4 types of prior surgery. Those who had undergone RV–PA connection and VSD closure were *repaired*, regardless of the status of the PAs and MAPCAs or whether any unifocalization or pulmonary arterioplasty had been performed. Any direct central AP connection was defined as an *AP window*. Any type of unifocalization (ie, complete or incomplete) with pulmonary blood flow supplied through a systemic-to-PA shunt was considered *unifocalization to a shunt*. Other palliative procedures, including RV–PA connection with an open VSD, were considered *other palliation*.

Patients who had undergone prior surgery elsewhere, even if it had been described as repair or unifocalization, often required substantial PA reconstruction consisting of augmentation, unifocalization of residual MAPCAs, or revision of prior surgical anastomosis of MAPCAs. The first surgical procedure at LPCHS in these patients was characterized as *revision unifocalization*. If a patient had undergone unifocalization to a shunt at an outside institution, options for the first LPCHS surgery included revision unifocalization, in which the pulmonary circulation would still be supplied by a shunt, or complete repair, which included PA reconstruction along with VSD closure and RV–PA conduit placement. In patients whose prior procedure was repair and who underwent revision unifocalization, the date of complete repair used for outcome analyses was set as the date of the first surgery at LPCHS.

Follow-Up and Reintervention

After complete repair, whether in a single stage or after palliation, we perform an echocardiogram and quantitative lung perfusion scintigraphy at hospital discharge, and we recommend repeating these studies every 3 months as a means of screening for early adverse remodeling of the reconstructed pulmonary circulation. We also recommend a routine cardiac catheterization 1 year after repair. Findings indicative of increasing RV pressure or progressive changes in the distribution of lung perfusion on noninvasive evaluation prior to 1 year generally merit earlier catheterization. During catheterization, even modest PA stenosis is typically treated with balloon angioplasty in an effort to optimize the uniformity of lung perfusion and PA pressure, even if central PA pressure is normal or low. Stent implantation is avoided. If there is more extensive or severe obstruction along with elevated central PA pressure, and balloon angioplasty does not provide sufficient relief, surgical revision is performed. Because of the volume of data necessary to present this experience, neither PA interventions between initial palliative surgery and complete repair nor reinterventions after complete repair were evaluated for this study.

Data Analysis

Data were presented as number (%) or median (quartile 1–quartile 3). For analysis, the cohort was considered in 3 configurations: (1) the entire 458-patient cohort; (2) patients who underwent their initial surgery at LPCHS (ie, not previously intervened on); and (3) patients who had complete repair at our center, either primarily or after prior palliation. Categorical variables were compared between groups using χ^2 analysis. Nonparametric comparison of continuous variables was performed using Wilcoxon rank-sum or Kruskal–Wallis tests. Time-related outcomes after first LPCHS surgery or after complete repair were depicted graphically with Kaplan–Meier curves. Assessment of factors associated with time-related outcomes was performed using Cox regression analysis. When indicated, factors significant to $P<0.05$ on univariable analysis were considered for inclusion in multivariable logistic or Cox regression models, with forward stepwise selection of variables using $P<0.05$. SPSS version 23 was used for statistical analysis. P values <0.05 were considered significant.

Results

From November 2001 to April 14, 2016, 458 patients with TOF and MAPCAs underwent surgery at LPCHS. Most of these patients had pulmonary atresia, but 34 had severe pulmonary valve stenosis. One or more prior surgical procedures had been performed elsewhere in 167 patients (36%), while the remaining 291 were primary LPCHS patients who underwent their initial surgery at our center.

Entire Cohort

A flow diagram for the full 458-patient cohort is depicted in Figure 2, and data are summarized in Table 1. Patients who had undergone prior surgery elsewhere were older at the time of the first LPCHS surgery than those managed initially at LPCHS, but were younger at the time of first surgery at any center (both $P<0.001$). There were no other significant demographic or diagnostic differences. Because anatomic data or imaging studies obtained prior to the outside interventions were not available for many of the previously treated patients, the native anatomy of the pulmonary circulation was often not known in detail to the investigators, so it was not possible to characterize or analyze features related to the PAs or MAPCAs.

Overall, 54% of the full cohort underwent single-stage complete repair at the first LPCHS surgery, while 11% had an AP window constructed, 21% had unifocalization to shunt or a similar palliation, and 14% had revision or augmentation of a prior PA reconstruction. The profile of first LPCHS surgery type differed between primary LPCHS and previously treated patients, largely because revision was the most common intervention in previously treated patients. An AP window was performed almost exclusively in primary LPCHS patients, in keeping with the management paradigm outlined in the Methods section.

Follow-up was documented a median of 3.0 years (0.6–7.9 years; mean 4.4 years) after the first LPCHS surgery, with 173 patients followed for >5 years and a total of 1987 patient-years of follow-up available. Estimated survival was 85±2% at 5 years after the first LPCHS surgery, and there were no differences according to whether patients had undergone prior surgery elsewhere. However, among the entire cohort, survival was significantly better among patients whose first LPCHS surgery was complete repair (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.25–0.77; $P=0.004$) than those who initially underwent palliation or revision (Figure 3). Patients with Alagille syndrome, although few in number, had a significantly higher risk of mortality over time than those with no known chromosomal anomalies (HR, 3.1; 95% CI, 1.2–7.7; $P=0.017$; Figure 3). Among patients whose first surgery was performed elsewhere, there was no difference in survival according to type of first LPCHS procedure.

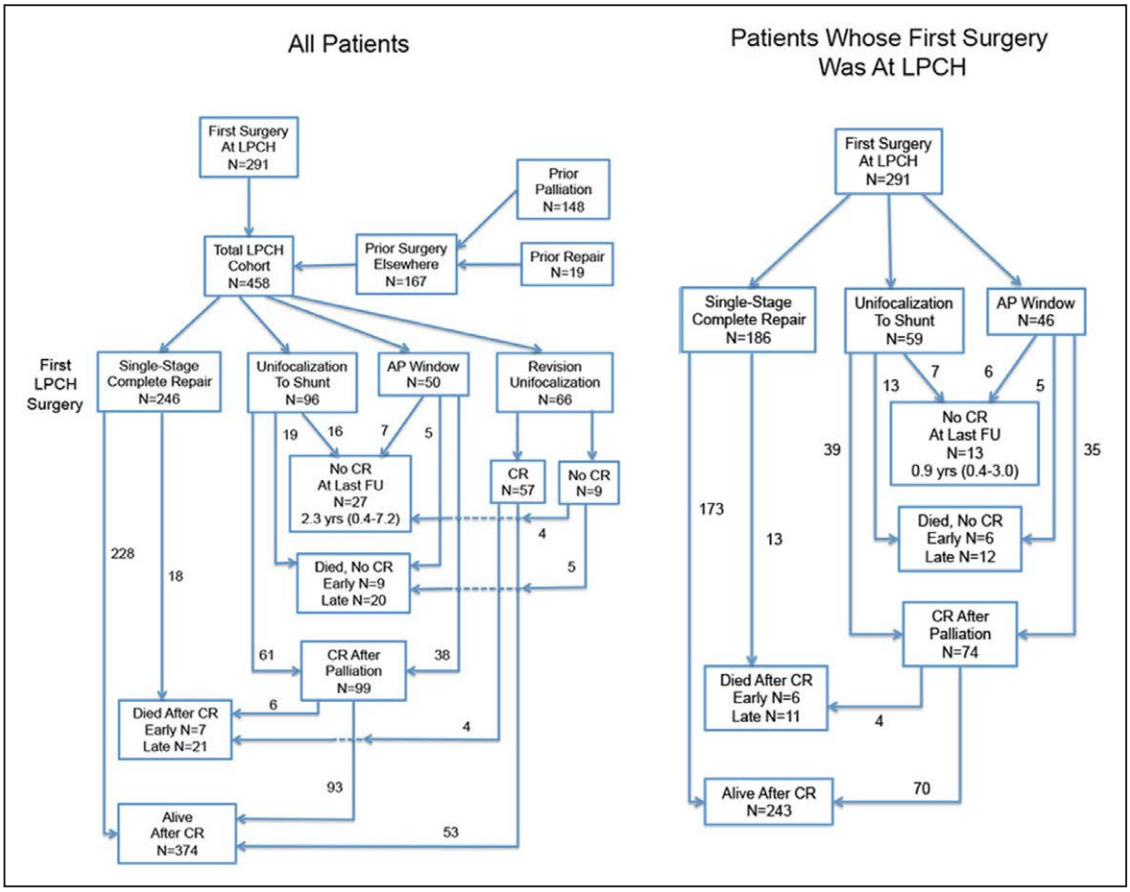

Figure 2. Flow diagrams summarizing management and outcomes of all patients treated during the study period (**left**) and only patients whose first surgery was performed at LPCHS (**right**). Surgical groups as defined in the Methods section. AP indicates aortopulmonary; CR, complete repair; FU, follow-up; and LPCHS, Lucile Packard Children's Hospital Stanford.

Table 1. All Patients With TOF and MAPCAs Undergoing Surgery at LPCHS

	Total (N=458)	First Surgery Performed at LPCHS (N=291)	First Surgery Performed Elsewhere (N=167)
Male	237 (52%)	150 (51%)	93 (56%)
Age at first surgery, mo	4.0 (1.3–7.3)	4.8 (2.1–7.6)	2.6 (0.6–7.2)
Age at first LPCHS surgery, mo	7.3 (3.5–37)	4.8 (2.1–7.6)	42 (13–96)
Known genetic abnormality			
Deletion chromosome 22q11	165 (36%) 69U*	109 (38%) 29U*	56 (34%) 40U*
Alagille syndrome	13 (2.8%)	9 (3.1%)	4 (2.4%)
Other chromosomal abnormality	6 (1.3%)	5 (1.7%)	1 (0.6%)
Native anatomy			
Valvar pulmonary stenosis (all others atresia)	34 (7.4%)	28 (9.6%)	6 (3.6%)
Confluent central PAs	290 (63%) 75U*	214 (74%)	NA
PDA supplying 1 lung	34 (7.4%) 69U*	28 (10%)	6 (3.6%)
First surgery type at LPCHS			
Complete unifocalization and repair	246 (54%)	186 (64%)	60 (36%)
Unifocalization to shunt or other palliation	96 (21%)	59 (20%)	37 (22%)
AP window	50 (11%)	46 (16%)	4 (2.4%)
Revision unifocalization after prior repair	66 (14%)	…	66 (40%)
Early outcomes after first LPCHS surgery			
Death	16 (3.5%)	11 (3.8%)	5 (3.0%)
Duration of ICU stay, days	9 (6–16)	9 (7–20)	7 (4–13)
Duration of hospitalization, days	15 (10–25)	17 (11–29)	13 (8–21)
Complete repair achieved by most recent FU	402 (88%)	260 (89%)	142 (85%)
Age, mo	8.6 (4.9–29)	6.4 (4.1–13.9)	44 (15–103)
As first surgery at LPCHS	246 (54%)	186 (64%)	60 (36%)
After palliative surgery at LPCHS	114 (25%)	74 (25%)	40 (25%)
Duration after first surgery at LPCHS, y		0.6 (0.4–1.4)	1.0 (0.6–2.2)
Number of MAPCAs unifocalized	3 (2–5)	4 (2–5)	3 (1–4)
Early outcomes after complete repair			
Duration of cardiopulmonary bypass, min	252 (191–325)	248 (191–320)	266 (195–336)
Systolic RV pressure, mm Hg	35 (30–39)	33.5 (29–38)	38 (33–40)
RV:AO systolic pressure ratio	0.35 (0.30–0.42)	0.35 (0.30–0.40)	0.37 (0.31–0.43)
Death	7 (1.7%)	6 (2.3%)	1 (0.7%)
Duration of ICU stay, days	9 (6–15)	9 (6–16)	8 (5–13)
Duration of hospitalization, days	15 (9.5–22)	16 (10–22)	12 (8–21)
Follow-up			
Duration after first LPCHS surgery, y	2.7 (0.5–7.6)	2.5 (0.5–7.3)	3.0 (0.3–8.6)
Duration after complete repair, y	2.7 (0.2–7.4)	2.6 (0.4–7.3)	2.7 (0.1–7.5)
Status at most recent FU			
Alive	401 (88%)	256 (88%)	145 (87%)
CR: alive	374 (82%)	243 (84%)	131 (78%)
Palliative circulation: alive	27 (6%)	13 (4%)	14 (8%)
Died after palliation: early/late	29; 9/20	18; 6/12	11; 3/8
Died after CR: early/late	28; 7/21	17; 6/11	11; 1/10
PA:AO systolic pressure ratio at FU after CR	0.40 (0.32–0.50)	0.39 (0.32–0.50)	0.43 (0.33–0.54)

Data presented as median (quartile 1–quartile 3) or number (%). AO indicates aortic; AP, aortopulmonary; CR, complete repair; FU, follow-up; ICU, intensive care unit; LPCHS, Lucile Packard Children's Hospital Stanford; MAPCAs, major aortopulmonary collateral arteries; mo, months; NA, not applicable/available; PA, pulmonary artery; PDA, patent ductus arteriosus; RV, right ventricle; TOF, tetralogy of Fallot; and U, unknown.

*Percentages are calculated using the entire column total, not the number with data that is known.

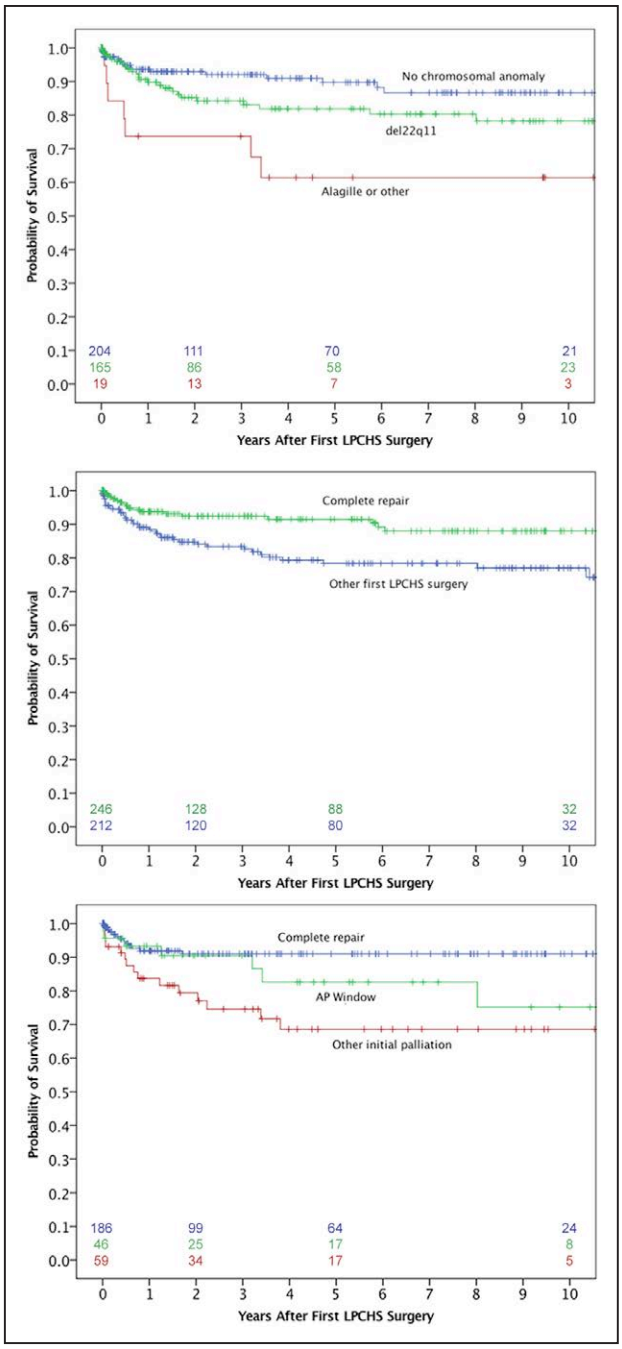

Figure 3. These Kaplan–Meier curves depict estimated survival after first LPCHS surgery. **Top** and **Middle**, Survival for the entire study cohort (**top**) according to the presence of chromosomal anomalies and (**middle**) according to whether the first LPCHS surgery was complete repair or another procedure. **Bottom**, Survival according to the first surgical procedure among the cohort whose initial surgery was at LPCHS. LPCHS indicates Lucile Packard Children's Hospital Stanford.

A total of 402 patients underwent complete repair either at the first LPCHS surgery or subsequently (Figure 2). Data on this cohort are summarized below. The Kaplan–Meier probability of complete repair for the entire cohort was 83% 1 year after the first LPCHS surgery and 93% at 5 years. Among patients who were palliated, the median duration from first LPCHS surgery to complete repair was 8.3 months (4.8–20.5 months) and was shorter for primary LPCHS patients than for those who underwent prior surgery elsewhere (7.1 months [4.2–15.2 months] versus 12.2 months [7.1–28.5 months]; *P*=0.001). Of the 56 patients who had not undergone complete repair, 29 were deceased (9 early after the first LPCHS surgery), and 5 were <1 year out from palliation and expected to be candidates for complete repair. Four of the early deaths were in high-risk neonates: 3 with hypercyanosis who were intubated prior to surgery and 1 with complete tracheal rings. Approximately 8 patients in the palliated cohort are not expected to become candidates for complete repair. For the most part, these patients underwent unifocalization to a shunt but continue to have little raw material for adequate distal PA reconstruction, with high total pulmonary resistance related to conduit vessel cross-sectional area and, in some cases, high pulmonary vascular resistance. The remaining patients continue to be evaluated for potential future interventions and ultimately may be suitable for repair.

A chromosome 22q11 deletion was documented in 164 patients, but the status was unknown in 69 of the 458 patients (15%). There were no differences in demographic or anatomic features, initial procedure performed, or achievement of complete repair between patients with and without a 22q11 deletion. As noted earlier, survival was worse in patients with a 22q11 deletion than those with no known chromosomal anomaly. Alagille syndrome was confirmed in 13 patients; only 2 of these patients underwent complete repair at the first LPCHS surgery, 8 ultimately achieved complete repair, and 5 died (4 after palliation). Other chromosomal anomalies were diagnosed in 6 patients: 1q23.1–23.3 deletion, unspecified chromosome 1 deletion, 6p24 deletion, 6q deletion, 15q14 homozygosity at 17.3, and 47 XXY. Overall, patients with Alagille syndrome or another chromosomal anomaly were less likely to undergo complete repair than those with no anomalies or a chromosome 22q11 deletion and had significantly worse survival (Figure 3).

Patients Who Underwent Initial Surgery at LPCHS

Among the 291 patients whose initial surgery was performed at LPCHS, 186 (64%) underwent single-stage complete repair, 46 (16%) had an AP window initially, and 59 (20%) were palliated with another procedure, most often with complete unifocalization to a shunt (Figure 3 and Table 2). Surgery was performed in the neonatal period in 15% of these patients (n=45; 15 complete repair, 19 AP window, and 11 other palliation). Patients who underwent palliation other than an AP window were more likely to have a chromosomal anomaly than those who underwent complete single-stage repair.

Early outcomes in the primary LPCHS cohort are summarized in Table 2. The duration of hospitalization after the first LPCHS surgery was significantly longer in patients whose initial procedure was palliation to a shunt than those who underwent complete repair or an AP window. There were more early deaths in this group as well, but the difference did not reach statistical significance. Survival over time for the 3 initial surgery types is depicted in Figure 3. Compared with patients who underwent single-stage complete repair, those whose initial procedure was unifocalization to a shunt or other palliation had worse survival after the first LPCHS surgery (HR, 3.4; 95% CI, 1.6–7.1; *P*=0.001). Patients who initially

Table 2. Patients Who Had First Surgery at LPCHS According to Type of First Surgery (N=291)

	Complete Unifocalization and Repair (N=186)	AP Window (N=46)	Other Palliation (N=59)	*P* Value
Age at first LPCHS surgery, mo	5.5 (3.1–8.6)	1.6 (0.4–3.3)	4.1 (2.4–7.2)	<0.001
Known genetic abnormality				
Deletion chromosome 22q11	65 (38%) 18U	15 (37%) 6U	29 (53%) 5U	0.12
Alagille syndrome	1 (0.5%)	4 (8.7%)	4 (6.8%)	0.004
Other chromosomal abnormality	3 (1.6%)	1 (2.2%)	1 (1.7%)	0.97
Native anatomy				
Valvar pulmonary stenosis	13 (7%)	9 (20%)	6 (10%)	0.04
Confluent central PAs	132 (71%)	45 (98%)	37 (63%)	<0.001
Early outcomes after first LPCHS surgery				
Death	5 (2.7%)	2 (4.3%)	4 (6.8%)	0.29
Duration of ICU stay, days	9 (7–16)	7 (4–13)	19 (9–35)	0.43
Duration of hospitalization, days	17 (11–25)	12 (9–22)	24 (15–54)	<0.001
Complete repair (CR) performed	186 (100%)	35 (76%)	39 (66%)	
Age, mo	5.4 (3.1–8.6)	8.6 (5.8–17.3)	12.6 (9.3–20.0)	<0.001
Duration from first LPCHS surgery, mo	…	6.5 (4.3–19.6)	7.1 (4.2–11.5)	
Number of MAPCAs unifocalized	4 (3–5)	3 (2–5)	3 (2–5)	0.086
Early outcomes after CR				
Duration of cardiopulmonary bypass, min	260 (203–326)	212 (168–288)	177 (137–289)	0.008
Systolic RV pressure, mm Hg	32 (28–35)	38 (31–40)	35 (30–37)	0.045
RV:AO systolic pressure ratio	0.34 (0.29–0.40)	0.38 (0.31–0.42)	0.38 (0.34–0.44)	0.097
Death	5 (2.7%)	1 (2.2%)	0 (0%)	0.37
Duration of ICU stay, days	9 (7–16)	8 (6–11)	10.5 (6–15)	0.16
Duration of hospitalization, days	17 (11–25)	13 (9–19)	16 (10–24)	0.016
Status at most recent FU				
Alive				
CR: alive	173	33	37	
Palliative circulation: alive	0	6	7	
Died after palliation: early/late	0; 0/0	5; 2/3	13; 4/9	
Died after CR: early/late	13; 5/8	2; 1/1	2; 0/2	
FU duration after first LPCHS surgery, years	2.3 (0.4–7.6)	3.1 (1.0–7.1)	2.6 (0.7–6.1)	
FU duration after CR, y	2.3 (0.4–7.6)	3.7 (0.4–6.3)	3.4 (1.2–6.1)	
PA:AO systolic pressure ratio at FU after CR	0.35 (0.29–0.42)	0.38 (0.33–0.49)	0.39 (0.33–0.49)	0.025

Data presented as median (quartile 1–quartile 3) or number (%). AO indicates aortic; AP, aortopulmonary; CR, complete repair; FU, follow-up; ICU, intensive care unit; LPCHS, Lucile Packard Children's Hospital Stanford; mo, months; PA, pulmonary artery; RV, right ventricle; and U, unknown.

underwent an AP window had intermediate survival over time, but did not differ from either of the other groups. The only other factor associated with a higher risk of mortality over time after the first surgery was chromosomal abnormalities: compared with patients with no known anomaly, those with a chromosome 22q11 deletion (HR, 2.8; 95% CI, 1.2–6.5; *P*=0.017) or with Alagille syndrome or another chromosomal anomaly (HR, 6.8; 95% CI, 2.4–20; *P*<0.001) were at higher risk. On multivariable analysis, unifocalization to a shunt (HR, 2.6; 95% CI, 1.2–5.8; *P*=0.016), chromosome 22q11 deletion (HR, 2.4; 95% CI, 1.1–5.6; *P*=0.043), and Alagille syndrome or other chromosomal anomaly (HR, 5.6; 95% CI, 1.9–17; *P*=0.002) were associated with worse survival.

Patients Who Had Undergone Prior Surgery Elsewhere

Among the 167 patients who were referred to LPCHS after surgery elsewhere, most had undergone palliation at the prior

procedure(s), although 11% had a repair (VSD closed fully or partially, RV connection to the PAs). In this cohort, the first surgical procedure performed (elsewhere) was repair in 19 patients (11%), unifocalization to a shunt in 41 (25%), an AP window in 29 (17%), and other palliation in 78 (47%). Among the 66 patients whose first LPCHS surgery was revision, 43 patients (65%) had a completely repaired circulation after the first LPCHS surgery. None of the details available, including first surgery type overall or first LPCHS surgery type, were associated with survival over time among this cohort.

Patients Who Underwent Complete Repair

Complete repair, including unifocalization and PA reconstruction, VSD closure, and RV–PA connection, was performed in 402 patients, either as a single-stage procedure at our center (n=186), after initial palliation at our center with either an AP window (n=35) or unifocalization to a shunt (n=39), or after prior surgery elsewhere followed by repair or revision at LPCHS (n=142) (Figures 4 and 5). Patients who underwent surgery before referral were older at repair than primary LPCHS patients (3.6 years [1.2–8.6 years] versus 0.5 years [0.3–1.2 years]; $P<0.001$). The median number of MAPCAs unifocalized was 3, and the median duration of cardiopulmonary bypass was 252 minutes, neither of which differed between primary LPCHS patients and those who had prior surgery.

The median RV:aortic pressure early after complete repair was 0.35 (0.30–0.42); only 4 patients had a ratio >0.6, and the highest ratio was 0.71. Primary LPCHS patients had a lower RV systolic pressure ($P<0.001$) and RV:aortic pressure ratio ($P=0.006$) early after repair than those who underwent prior surgery elsewhere (Table 1). Variables associated with an early postrepair RV:aortic pressure ratio ≥0.35 are summarized in Table in the Data Supplement.

Seven patients (1.7% of 402) died early after complete repair. The median duration of follow-up after complete repair was 3.0 years (0.5–7.7 years; mean 4.3 years), and the total follow-up was 1702 patient-years. Survival over time after complete repair is depicted in Figure 6 and was 92±2% at 5 years after repair. Factors associated with higher risk of mortality over time after complete repair included chromosomal anomalies, older age at repair, a greater number of MAPCAs unifocalized, and higher absolute and relative RV pressure early after repair (Table 3 and Figure 6). There were no differences in survival after complete repair according to whether patients had undergone prior surgery elsewhere or had native confluent PAs.

Discussion

In our programmatic experience, 458 patients with TOF and MAPCAs have undergone treatment over the past 15 years, including 291 whose first surgery was performed at our center. Almost 90% of patients underwent complete repair, either as a single-stage complete unifocalization and repair (n=186), after primary palliation at our center (n=74), or after prior surgery elsewhere (n=142). Early mortality after both palliation and complete repair was low, as were RV pressures among patients who underwent complete repair. Patients undergoing complete single-stage unifocalization and repair had the best outcomes overall, including shorter length of stay, better survival, and lower RV pressure.

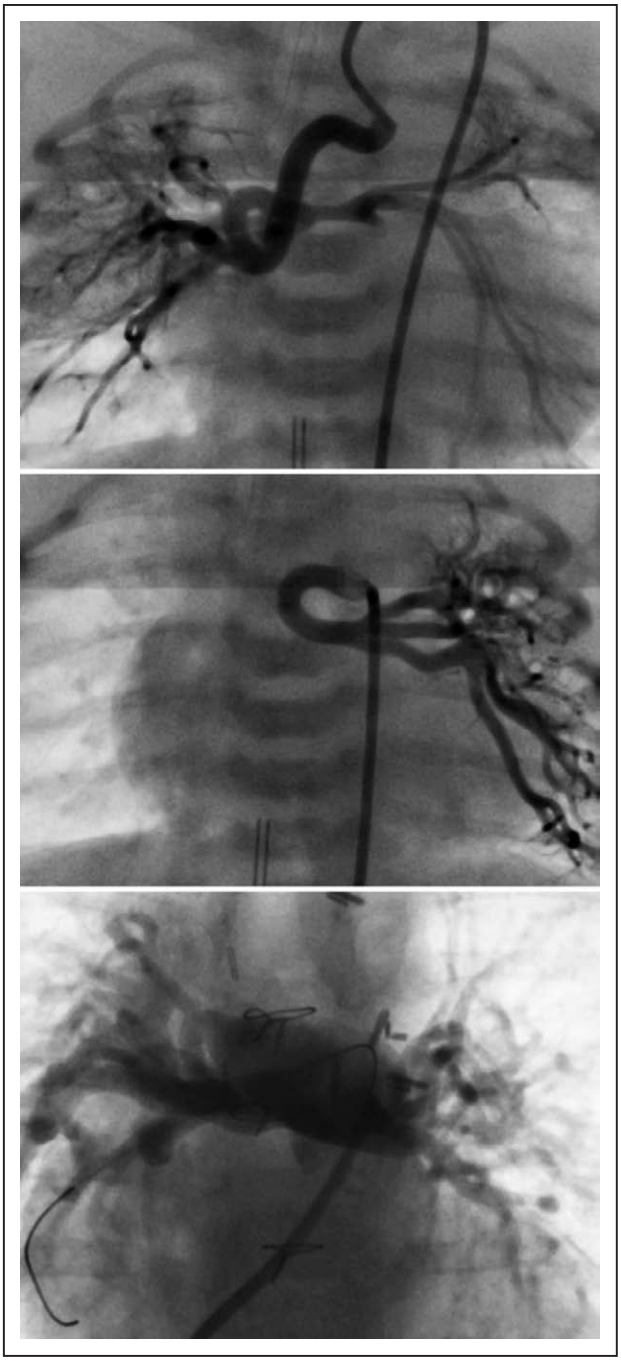

Figure 4. Pre- and postoperative angiograms in a patient who underwent complete single-stage unifocalization and repair in infancy. **Top**, Selective preoperative angiogram of a dual-supply collateral that feeds into the central pulmonary arteries. **Middle**, Selective preoperative angiogram of a single supply collateral to the remainder of the left lung. **Bottom**, Angiogram in the RV-pulmonary artery conduit 1 year after repair demonstrates the reconstructed pulmonary arterial anatomy, which was characterized by relatively proximal branching of segmental and subsegmental vessels that were somewhat small in caliber but without significant stenosis (central PA pressure 34/13 mm Hg, PA:aortic pressure ratio 0.41). PA indicates pulmonary artery; and RV, right ventricle.

The prognostic importance of total cross-sectional PA area and early postoperative RV:aortic pressure ratio after repair in patients with TOF and pulmonary atresia was established

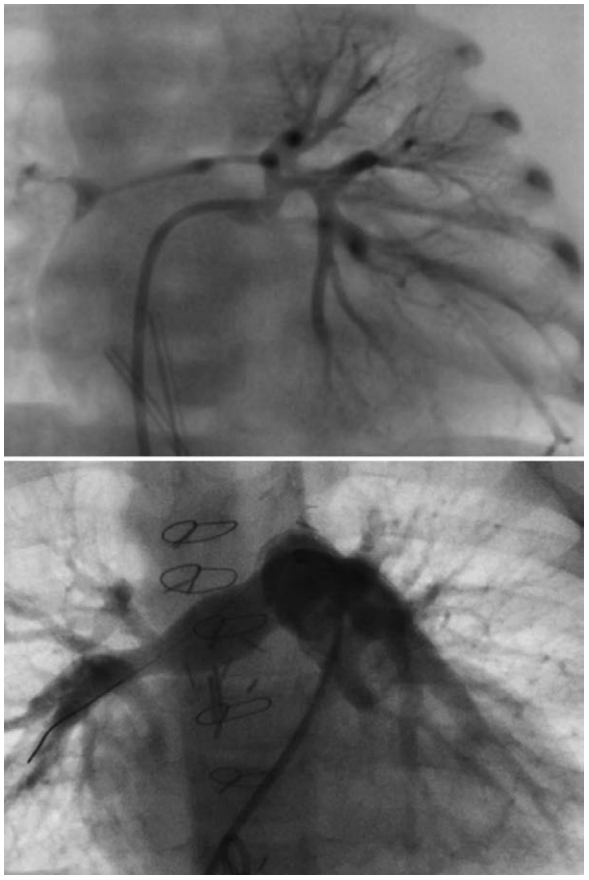

Figure 5. Top, Preoperative angiogram in a patient with 6 dual-supply MAPCAs who subsequently underwent an AP window as the initial procedure, followed by complete repair at 6 months of age. The postoperative RV:aortic pressure ratio was 0.28. At time of complete repair, the ICU stay was 7 days, with a total hospital stay of 12 days. **Bottom**, This postoperative angiogram 1 year after repair demonstrates the reconstructed pulmonary arteries. The RV:aortic pressure ratio at this catheterization was 0.30. AP indicates aortopulmonary; ICU, intensive care unit; MAPCAs, major aortopulmonary collateral arteries; and RV, right ventricle.

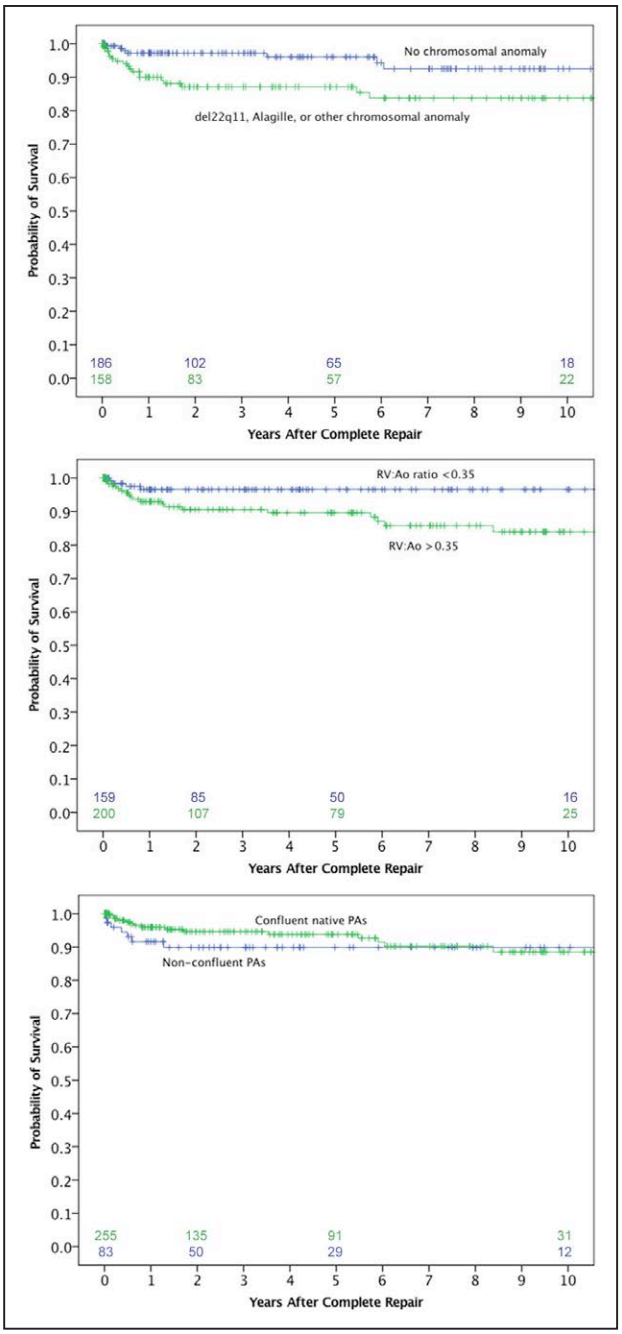

Figure 6. These Kaplan–Meier curves depict estimated survival after complete repair, according to (**top**) the presence of chromosomal anomalies, (**middle**) the early postrepair RV:aortic pressure ratio, and (**bottom**) confluent or nonconfluent native PAs. PA indicates pulmonary artery; and RV, right ventricle.

in the pioneering studies from Kirklin's group.[8,19,20] Although those studies included patients with TOF and pulmonary atresia, who had duct-dependent but normal PAs, this concept has also been applied to the more complex group of patients with MAPCAs. Optimizing these 2 variables is central to our management approach, which emphasizes complete incorporation of the blood supply to all lung segments, anatomically appropriate reconstruction and augmentation of the PA tree, and ensuring low total pulmonary resistance (and, hence, low RV pressure) before completing the repair. In the cohort of patients who underwent complete repair in this series, the median RV:aortic pressure ratio early after repair was 0.35 and was even lower for patients in whom single-stage complete repair was performed. This corresponded to an absolute RV systolic pressure of 35 mm Hg. It is worth noting that this ratio is for a cohort repaired at a median age of 8.6 months, which is much younger than that in the studies by Kirklin's group and others. Accordingly, the RV:aortic pressure ratio, although substantially lower than in other series,[5,6,10,12,21] may not be directly comparable, insofar as younger patients tend to have lower systemic pressures, which may bias toward higher ratios. Although early postoperative RV pressures were low in this series, higher RV:aortic pressure ratios after complete repair were still associated with a greater risk of mortality over time within our cohort.

Our programmatic algorithm for management of the neonate with TOF and MAPCAs has been discussed in prior reports and summarized above.[22,23] Utilization of an intraoperative flow study for decision-making about complete repair, in which a dedicated pump from the bypass machine is used

Table 3. Factors Associated With Mortality After Complete Repair Surgery Among the Entire Cohort

Variable	Univariable, HR (95% CI)	*P* Value	Multivariable, HR (95% CI)	*P* Value
Chromosomal abnormality				
None	Ref			
Chromosome 22q11 deletion	2.9 (1.2–7.0)	0.019		
Alagille syndrome or other chromosomal abnormality	3.6 (0.7–17)	0.10		
Age at complete repair, y	1.05 (1.01–1.10)	0.034		
Systolic RV pressure early after repair, mm Hg*	1.08 (1.00–1.17)	0.047		
RV:aortic pressure ratio ≥0.35 early after repair	5.3 (1.2–22.7)	0.023	9.6 (1.2–73)	0.028
Number of MAPCAs unifocalized	1.30 (1.05–1.61)	0.017		

CI indicates confidence intervals; HR, hazard ratio; MAPCAs, major aortopulmonary collateral arteries; Ref, reference group; and RV, right ventricle.

*Because RV pressure and RV:aortic pressure ratio were collinear, RV pressure was not included in the multivariable model.

to increase flow to the unifocalized pulmonary circulation gradually while measuring mean pressure, effectively allowing calculation of total pulmonary resistance, has been vital to differentiation of good candidates for complete repair from those who will be better served by intermediate palliation with a shunt.[24] Others have also reported the utility of intraoperative evaluation of pulmonary resistance in this population.[25] The value of this simulation is evidenced by the fact that no patients in this series underwent complete repair and subsequently required takedown or fenestration of the VSD patch. In a previous report of our experience at a different center, 5% of patients who underwent complete single-stage unifocalization had an early reoperation either to close or reopen a VSD.[18] This prior experience is precisely the reason for utilization of the intraoperative flow study in our more recent practice, and as illustrated in this series, the utility of this approach has proven invaluable for deciding on VSD closure.

In contrast to our earlier approach, and to the method favored by others,[5,6,11,12,21] we no longer unifocalize pulmonary blood supply to an RV–PA conduit and leave the VSD open. Rather, we have shifted our approach to providing pulmonary blood flow through a central shunt in patients who are unifocalized but do not receive a complete repair at the same stage, and we think this approach, which was practiced exclusively in this series, adds to the overall success in these patients, as previously reported.[18,26] With an RV–PA conduit and an open VSD, patients may be subject to pulmonary overcirculation that can lead to substantial morbidity and reintervention or occasionally to pulmonary vascular disease, and in our prior experience, we also observed relatively frequent formation of RVOT pseudoaneurysms. A central systemic-to-PA shunt provides a more predictable and protected source of pulmonary blood flow and can be performed without cross-clamping. A vital element of this approach, which was not evaluated in this study but was discussed earlier, is adequate imaging to identify important physiological and anatomic drivers of treatment choice.

Worse outcomes in patients with TOF and chromosomal abnormalities, particularly 22q11 deletion or a *JAG 1* mutation, were reported previously.[3,27,28] This was also the case in our cohort. Specific factors contributing to the increased risk in this population were not elucidated, and this remains an important area for investigation. The cohort of patients with Alagille syndrome has proved particularly challenging, with 5 deaths in 13 patients and almost universal reintervention on the PAs among the subset who had a complete repair. While PA reconstruction in patients with Alagille syndrome without MAPCAs has been successful at our institution, outcomes are less favorable in those with TOF and MAPCAs. Longer-term outcomes among patients who undergo complete repair will require additional study. Moreover, further work is needed to identify anatomic or systemic risk factors, including the anatomy of the pulmonary blood supply, respiratory/pulmonary pathophysiology, immunologic susceptibility, and so on, that may contribute to adverse outcomes in patients with these and potentially other chromosomal abnormalities.

There are several additional important findings from this study. Notably, several factors that have been considered poor prognostic factors or that we suspected would be associated with worse outcomes did not prove to be risk factors. For example, although survival over time was significantly better among patients whose first LPCHS surgery was complete unifocalization and repair, there were no differences in early or time-related survival or successful complete repair after the first LPCHS surgery according to whether patients had undergone prior surgery elsewhere. Also, as found in a recent study,[29] absence of true central PAs was not associated with any significant difference in outcomes, including likelihood of single-stage complete repair, postrepair RV pressure or RV:aortic pressure ratio, or survival. Some approaches to management of TOF with MAPCAs emphasize rehabilitation of the central PAs and de-emphasize the importance of MAPCAs, regardless of anatomy, and it has been our experience that some physicians are under the impression that treatment options are limited and the prognosis worse for patients without true central PAs. However, this study and our prior report demonstrate that outcomes are comparably good with our approach irrespective of the presence of confluent mediastinal PAs.

The complexity of TOF with pulmonary atresia and MAPCAs revolves primarily around the anatomy and function of the pulmonary circulation. Part of this complexity stems from the incredible heterogeneity of the vessels supplying the lungs and from the difficulty in integrating the multiple aspects of this variability into a systematic nomenclature of classification that can be used to simplify and focus both management and communication. While specific characteristics of the PA or MAPCA anatomy may well impart or ameliorate risk in our population, it is challenging to identify such an impact because of the multitude of variable features and

the sheer number of patterns and particularities. Because of a combination of the practical and analytic challenges of defining, cataloging, and considering the variability of the pulmonary circulation, we did not incorporate such features into this analysis. The few anatomic characteristics that we did consider were those that we were able to ascertain consistently and clearly in all or most cases, such as the patency of the pulmonary valve, the presence of confluent central PAs, or supply of one lung through a PDA or an anomalous PA from the ascending aorta. For example, we did not consider the number of MAPCAs per se, which depends on how they are quantified (ie, number originating from the systemic circulation, major branches if the primary MAPCAs divides before entering the lung), but rather the number of MAPCAs anastomosed during the unifocalization. Similarly, although patients undergo different primary procedures depending on the specific anatomic and physiological features, it is methodologically confounding to compare these treatment groups. In this study, comparison between patients whose first LPCHS surgery was complete repair, an AP window, or unifocalization to a shunt (or other palliation) was not intended as an evaluation of one management strategy against another, but rather as a comparison of patient/anatomy type, insofar as different procedures were performed depending on the anatomy and physiology of the pulmonary circulation.

Limitations

This retrospective study included patients referred from multiple institutions, many of whom had undergone interventions prior to referral to LPCHS. As a result, native anatomic details were unknown for some patients, and details of follow-up management at outside institutions were not always available. In addition, patients underwent a variety of first procedures, and comparative analysis of outcomes after different interventions is not always practical or meaningful (eg, the RV:aortic pressure ratio is not an informative outcome measure after palliation to a shunt or an AP window in which the VSD is open, whereas it is critically important after complete repair). Thus, the analysis of longer-term outcomes was focused primarily on patients who underwent complete repair, either in a single stage or after palliation. The duration of follow-up in patients managed elsewhere was variable, which may have introduced various types of bias. This study does not allow us to understand how the reconstructed PAs may remodel (favorably or adversely) over time; however, the observation that the large cohort of patients with absent central PAs, whose infant reconstruction included only MAPCAs and patch tissue, continue to do as well as other patients in this overall experience provides compelling evidence that early incorporation of MAPCAs allows these vessels to grow effectively over time.

This study did not evaluate reinterventions after complete repair, which is a topic of importance and interest that warrants more detailed investigation than can be addressed in this broad overview. A separate study evaluating reinterventions on the pulmonary circulation after these procedures is planned.

Conclusions

Using a programmatic approach that emphasizes early complete unifocalization and repair with incorporation of all lung segments and extensive lobar and segmental PA reconstruction, we have achieved excellent results both in patients with native disease and who have undergone various interventions prior to referral to our center. Patients with chromosomal anomalies experience comparatively worse (but still excellent) outcomes, and we are actively investigating approaches to anticipatory evaluation and management aimed at understanding and mitigating noncardiac factors that may contribute to morbidity and mortality in that population. There remains much to be learned about longer-term outcomes in these patients, and several prospective studies are planned at our center in this unique patient population.

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Disclosures

None.

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Programmatic Approach to Management of Tetralogy of Fallot With Major Aortopulmonary Collateral Arteries: A 15-Year Experience With 458 Patients

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Supplemental Material

Supplemental Table. Factors associated with early post-repair RV:aortic pressure ratio ≥0.35

	OR (95% CI)	P value
Known genetic abnormality		0.015
None	Ref	
Deletion chromosome 22q11	1.7 (1.1-2.7)	0.010
Alagille syndrome/other	4.0 (0.8-19)	0.08
First LPCHS surgery type		0.005
Complete repair	Ref	
Unifocalization to shunt	2.1 (1.1-4.0)	0.018
AP window	1.7 (0.8-3.5)	0.19
Revision unifocalization	0.7 (0.4-1.5)	0.31
Palliative surgery before complete repair	2.0 (1.3-3.1)	0.001

AP, aortopulmonary; CI, confidence intervals; HR, hazard ratio; LPCHS, Lucille Packard Children's Hospital Stanford; Ref, reference group