Outcomes of Surgery for Simple Total Anomalous Pulmonary Venous Drainage in Neonates

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Background. **Repair of total anomalous pulmonary venous drainage (TAPVD) in neonates remains a challenge as it is often associated with severe obstruction. We describe a large cohort of neonates who underwent TAPVD repair at a single institution.**

Methods. **From 1973 to 2008, 112 patients underwent simple TAPVD surgery during the first month of life. Data collection occurred retrospectively.**

Results. **Preoperative pulmonary venous obstruction (PVO) occurred in 89 (79.5%) patients. There were 12 (10.7%) early deaths. Significant risk factors were bypass time greater than 65 minutes ($p = 0.014$) and emergent surgery ($p = 0.005$). Hospital mortality was unchanged throughout the 3 eras (1973 to 1988, 1989 to 1998, 1999 to 2008), despite an increase in patients with preoperative acidosis ($p = 0.004$) and severe TAPVD obstruction ($p = 0.038$) during the recent 10 years. There were 6 (6.25%) late deaths within 2 years of repair. Survival at 20 years was 83.4% (95% confidence interval 75 to 89). Risk factors for late death were operative weight 2.5 kg or less ($p = 0.004$) and postoperative pulmonary hypertensive crisis ($p = 0.02$). Reoperation for recurrent PVO was required in 13 patients (11.9%). Risk factors were operative weight 2.5 kg or less ($p = 0.035$) and postoperative pulmonary hypertensive crisis ($p = 0.002$). Follow-up was 96% complete and survivors (n = 90) were asymptomatic at a median age of 11.7 years.**

Conclusions. **Hospital mortality remained unchanged over the 36-year period. Survival beyond 2 years offers excellent outcome. Risk factors for mortality were the preoperative clinical status, prolonged bypass time, persisting micro-obstruction, and low operative weight. A reduction in mortality will likely require development of effective medical management for patients who have peripheral PVO not amenable to surgical repair.**

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Total anomalous pulmonary venous drainage (TAPVD) is an uncommon congenital heart anomaly that comprises approximately 1.5% of all congenital heart defects [1]. Since the first surgical attempt to correct TAPVD was reported in 1951 [2], improved surgical techniques and hospital care have led to significantly better outcomes of TAPVD surgery in children [3, 4]. However, a review of the literature suggests that neonates represent the most severe end of the TAPVD spectrum and may have higher rates of death [5–7]. Unfortunately, the outcomes reported in the literature contain a mix of both neonates and older patients. Hence, it is impossible to determine the true outcomes in neonates. We reviewed all neonates who underwent repair of TAPVD at a single institution in order to define the risk factors for and incidence of death and reoperations.

Patients and Methods

Patients

The present study was approved by the institutional Research Ethics Board. All patients who underwent surgery for TAPVD at the Royal Children's Hospital within the first month of life from 1973 to 2008 were identified. There were 112 patients who had simple TAPVD surgery during the neonatal period. The TAPVD patients with cardiac anomalies other than an atrial septal defect, patent ductus arteriosus, or ventricular septal defect were excluded. Data were obtained by review of medical records from initial admission until the last follow-up. The patients were followed with intervals from 3 to 6 months with echocardiogram during the first 2 years after surgery, followed by annual assessment. All pa-

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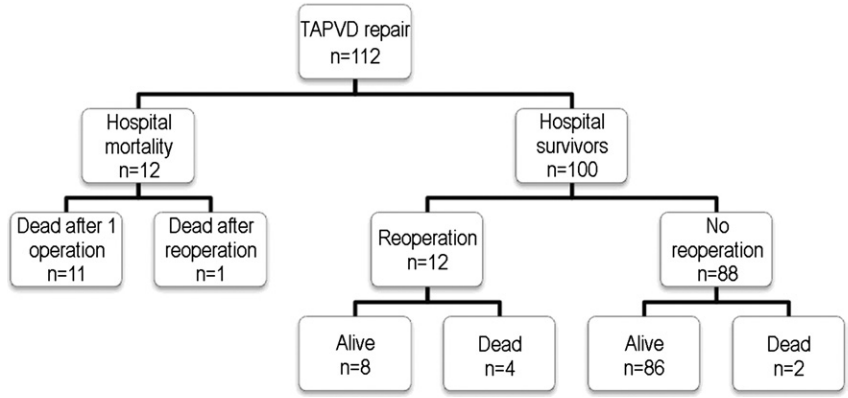

Fig 1. Flow-chart of events after total anomalous pulmonary venous drainage (TAPVD) repair (n = number of patients).

tients (n = 13) (Fig 1) who developed recurrent pulmonary venous obstruction (PVO) had angiogram prior to reoperation. Initial patient characteristics are presented in Table 1.

Definitions

A pulmonary hypertensive crisis was defined as having at least 1 event in which pulmonary arterial systolic pressure equaled or exceeded systemic levels followed by a rapid fall in systemic arterial pressure. Obstruction was confirmed by echocardiography and was evident clinically in each patient. Urgency of surgery has been categorized as below. Emergent surgery was defined as life-saving surgery. Urgent surgery was defined as surgery required within 24 to 48 hours of diagnosis. Patients who were outside the above-mentioned categories and deemed stable were classified as nonurgent. Acidosis was defined as having an arterial pH of less than 7.35 immediately prior to surgery. Prematurity was defined as birth at less than 37 weeks of gestation. Hospital mortality was defined as death occurring within 30 days of surgery or prior to hospital discharge. Late mortality was defined as death occurring after discharge or more than 30 days after TAPVD surgery. Recurrent PVO was defined as obstruction of the pulmonary veins as identified by echocardiogram, developing at any time after surgery. Reoperation was performed in symptomatic patients with documented PVO. It was further subdivided into recurrent PVO that develops at the site of anastomosis (anastomotic stricture) or distant from the site of anastomosis.

Patients were considered lost to follow-up if no information was available after their hospital discharge. The variables analyzed with respect to outcomes (death and reoperation) are listed in the Appendix.

Data Analysis

All data were analyzed with Stata version 10 (Stata Corp, College Station, TX). Data were expressed as mean ± standard deviation and median with interquartile (IQ) range as appropriate. Inferential comparisons were made using the Fischer exact test, Pearson χ^2 test, Mann-Whitney test, and the 2-sample mean comparison *t* test where appropriate.

Kaplan-Meier actuarial survival curves were used to analyze and plot time-related endpoints. Potential risk factors for binary outcomes (hospital mortality and late mortality) were identified by logistic regression analysis. Patients lost to follow-up were excluded from logistic regression analysis for late mortality. Cox proportional hazards analysis was used to identify hazards for time-related outcomes (reoperation for PVO). A *p* value of 0.08 was used for variable inclusion and exclusion on multivariable analysis. Backward stepwise methods were used such that variables were removed until all *p* values in the multivariable model were significant. All tests were 2-tailed and *p* values of less than 0.05 were considered significant.

Results

Preoperative pulmonary venous obstruction occurred in 89 (79.5%) patients. Infracardiac TAPVD was the most common to be obstructed (n = 48; 98.0%, 48 of 49). Of the patients with supracardiac anatomy, 68% had obstruction (n = 34; 34 of 50). In cardiac TAPVD, 50% of patients had obstruction (n = 6; 6 of 12) and the only patient with mixed TAPVD had obstruction (100%, 1 of 1). There were no differences in hospital mortality, late mortality, or reoperations in patients who had obstructed TAPVD compared with those who did not.

Operative Technique

Surgery was performed with standard cardiopulmonary bypass (CPB) and circulatory arrest was employed if required. Median CPB time was 61 minutes (IQ 42 to 98). Circulatory arrest was used in 82 patients with a median time of 31 minutes (IQ 25 to 36). The mean lowest temperature during CPB was 20°C ± 4.9°C. Care was taken to minimize handling of the pulmonary veins and avoid trauma to the pulmonary venous orifices. Standard side-to-side anastomosis was achieved for all cases and most had vertical vein ligation (n = 93; 93 of 99). Sutureless repair was performed in 3 patients during reoperation and standard redo side-to-side anastomosis was used in the remaining 10 patients. All patients had pulmonary artery and left atrial pressures monitored for at least 48 hours after surgery.

Table 1. Preoperative Characteristics of 112 Patients

Variable	No. (%) or Mean ± SD (Range)
Demographics:	
Male:female	76:36
Median age at surgery in days (IQ range)	5.0 (2–12)
Weight at surgery in kg	3.26 ± 0.6 (1.6–5.0)
<2.0 kg	2 (1.79)
2.0-2.5 kg	16 (14.3)
>2.5 kg	94 (83.9)
Length at surgery in cm	50.7 ± 3.0 (42.0–57.0)
BSA in m^2	0.21 ± 0.028 (0.13–0.37)
Diagnosis:	
Prematurity	11 (9.8)
Preoperative cardiac arrest	2 (1.79)
Preoperative acidosis	28 (25)
Mean pH on admission to hospital (range)	7.37 ± 0.12 (6.93–7.64)
Mean pH immediately prior to surgery (range)	7.42 ± 0.15 (6.88–7.66)
Preoperative obstruction	89 (79.5)
ASD	112 (100)
PDA	85 (75.9)
VSD	8 (7.1)
Bilateral SVC	2 (1.79)
Anatomical type:	
Supracardiac	50 (44.6)
Cardiac	12 (10.7)
Infracardiac	49 (43.8)
Mixed	1 (0.89)
Interventions:	
Preoperative intubation	80 (72.1)
Balloon atrial septostomy	9 (8.04)
Preoperative ECMO	1 (0.89)
Previous operation	3 (2.68)
PDA ligation	1 (0.89)
Noncardiac	2 (1.79)

ASD = atrial septal defect; BSA = body surface area; ECMO = extracorporeal membrane oxygenation; IQ = interquartile range; PDA = patent ductus arteriosis; SVC = superior vena cava; VSD = ventricular septal defect.

Hospital Mortality

Hospital mortality was 10.7% (n = 12; 12 of 112) (Fig 1). Low cardiac output due to heart failure was the cause of death for 8 patients (8 of 12). One died (1 of 12) due to pulmonary hypertensive crisis. Two other patients (2 of 12), who could not be weaned from mechanical ventilation, died of respiratory failure after therapy was ceased upon parental request. Bacterial sepsis caused death in 1 patient (1 of 12).

Table 2 describes the breakdown of results according to 3 consecutive eras (1973 to 1988, 1989 to 1998, and 1999 to 2008). There were no significant differences in the hospital mortalities of the 3 eras (p = 0.947). Variables compared among the 3 eras showed no significant difference in the incidence of preoperative PVO (p = 0.383) and prematurity (p = 0.667). The latest era showed no difference in mean operative weight (p = 0.066) and median age at surgery (p = 0.902) when compared with the earlier 2 eras. When the last 10 years (1999 to 2008) was compared with the earlier eras, there were significantly more emergent cases than urgent cases (p = 0.038) and more patients who had acidosis prior to surgery (p = 0.004). There were also significantly fewer interstate patients in the latest era (p = 0.018).

By multivariable logistic regression analysis, the following variables were identified to be independent risk factors for hospital mortality (Table 3): CPB time greater than 65 minutes (p = 0.014; odds ratio: 7.81; 95% confidence interval [CI]: 1.52 to 40.3) and urgency of surgery (p = 0.005; odds ratio: 9.13 for each category increase; 95% CI: 1.95 to 42.8).

Late Mortality

Follow-up was available for 96% of the operative survivors (n = 96; 96 of 100) for a median period of 10.9 years (1.5 months to 31.7 years). Four patients were lost to follow-up. These 4 patients did very well and had an uneventful postoperative course; 2 of them had obstruction and urgent surgery, 3 had preoperative weight above 2.5 kg, none had preoperative acidosis or postoperative pulmonary hypertensive crisis, or CPB time greater than 65 minutes. Thus, it is unlikely that these patients would contribute to significant informative bias. There were 6 (6.25%, 6 of 96) late deaths at a median time of 8.0 months (1.64 months to 15.5 months) after TAPVD repair. These included 5 deaths before 1 year and 1 death at 15.5 months. Two 33.3% (2 of 6) patients died of respiratory failure; the remaining 4 patients died of heart failure. Multivariable logistic regression analysis suggested the following risk factors for late mortality (Table 3): operative weight less than or equal to 2.5 kg (p = 0.004; odds ratio: 30.2; 95% CI: 2.95 to 309.9) and at least 1 postoperative episode of pulmonary hypertensive crisis (p = 0.02; odds ratio: 17.4; 95% CI: 1.57 to 192.1). The overall mortality of this series was 16.1% (n = 18; 18 of 112). Kaplan-Meier analysis demonstrated actuarial survival of 83.4% (95% CI: 75.0% to 89.2%) at both 10 and 20 years (Fig 2). Of the 18 deaths, histologic examination of the lungs was available for 12 patients. Thickened pulmonary vessel walls were found in 5 patients, pulmonary lymphangiectasia in 3 patients, a combination of both in 2 patients, and normal findings in 2 patients.

Reoperation for Pulmonary Venous Obstruction

There were a total of 16 reoperations for PVO in 13 patients (11.9%, 13 of 109). Freedom from reoperation for PVO (Fig 3) at 10, 15, and 20 years was 89.8% (95% CI: 81.9% to 94.4%), 85.4% (95% CI: 74.7% to 91.8%), and 82.7% (95% CI: 70.4% to 90.2%), respectively. Multivariable Cox proportional hazards analysis identified the following risk factors to be predictive of reoperation for PVO (Table 3): operative weight less than or equal to 2.5 kg (p = 0.035; hazard ratio: 3.62; 95% CI: 1.09 to 12.0) and at least one postoperative episode of pulmonary hyper-

Table 2. Hospital Mortality and Patient Characteristics According to Era

Mortality	Preoperative Obstruction	Emergent Surgery	Mean Weight at Surgery in kg	Median Age at Surgery in Days
1973–1988				
4/38 (10.5%)	33/38 (86.8%)	13/38 (34.2%)	3.18 (2.05–4.4)	8 (2–12)
1989–1998				
4/41 (9.8%)	31/41 (75.6%)	11/42 (26.2%)	3.20 (1.6–4.16)	4 (2–10)
1999–2008				
4/33 (12.1%)	25/33 (75.8%)	16/33 (48.5%)	3.43 (2.0–5.0)	4 (1–15)

tensive crisis ($p = 0.002$; hazard ratio: 6.19; 95% CI: 1.95 to 19.7).

The times to reoperation for anastomotic stricture (n = 4) were 1.7 months, 10.1 years, 14.6 years, and 15.1 years. There were no deaths after reoperation. The median time to reoperation for PVO distant from the site of anastomosis (n = 9) was 2.56 months (0.13 months to 1.03 years). All 9 patients had thickening of pulmonary veins; 8 patients had at least 2 veins obstructed and 1 patient had obstruction of a single vein. There were 5 patients (55.6%, 5 of 9) who died.

Functional Status

At the last follow-up, 90 of the 96 patients were alive at a median age of 11.7 years (1.81 months to 31.7 years). New York Heart Association (NYHA) functional class I was described in 82 patients (91.1%, 82 of 90), NYHA class II in 4 patients (4.44%, 4 of 90), and NYHA class was unknown in 4 patients (4.44%, 4 of 90).

Comment

Existing studies of outcomes in children undergoing TAPVD repair do not distinguish between neonates and older children. Hence, the current knowledge of TAPVD surgery in neonates is fragmented throughout the literature and limited to a small study and case reports [8–10]. Clearly, patients presenting with critical obstruction during the neonatal period represent the most severe end of the disease spectrum and can be expected to have higher mortalities [6]. This study has determined the outcomes of neonates and reported the experience gained at a single institution.

Most patients had obstructed TAPVD (79.5%). This accounted for the neonatal presentation and the high proportion of infants needing urgent surgery. In our study of neonates, there was a greater proportion of infracardiac TAPVD patients (43.8%) compared with the reported incidence of 15% to 25% in patients of all age groups [11]. This study confirmed previous findings that infracardiac TAPVD is more likely to be obstructed (98.0%, 48 of 49) [12, 13] and as such requires repair earlier in the neonatal period.

Hospital Mortality

Hospital mortality of less than 5% has been observed since 1995 in all age groups [6, 14]. However, neonates present the most difficult subgroup of the patients with

Table 3. Univariable and Multivariable Regression Analysis

	Univariable	Multivariable		
Variable	p Value	p Value	Odds Ratio	95% CI
Hospital mortality				
CPB time >65 minutes	0.01	0.014	7.81	1.52–40.3
Urgency of surgery	0.004	0.005	9.13	1.95–42.8
Prematurity	0.078			
Preoperative acidosis	0.002			
Age at surgery	0.07			
Late mortality				
Operative weight ≤ 2.5 kg	0.002	0.004	30.2	2.95–309.9
Postop pulmonary hypertensive crisis	0.013	0.02	17.4	1.57–192.1
Prematurity	0.001			
Other surgery during hospital stay	0.053			
Reoperation for PVO				
Operative weight ≤ 2.5 kg	0.057	0.035	3.62	1.09–12.0
Vertical vein ligation	0.017			
Cross-clamp time (minutes)	0.008			
Postop pulmonary hypertensive crisis	0.003	0.002	6.19	1.95–19.7

CI = confidence interval; CPB = cardiopulmonary bypass; PVO = pulmonary venous obstruction.

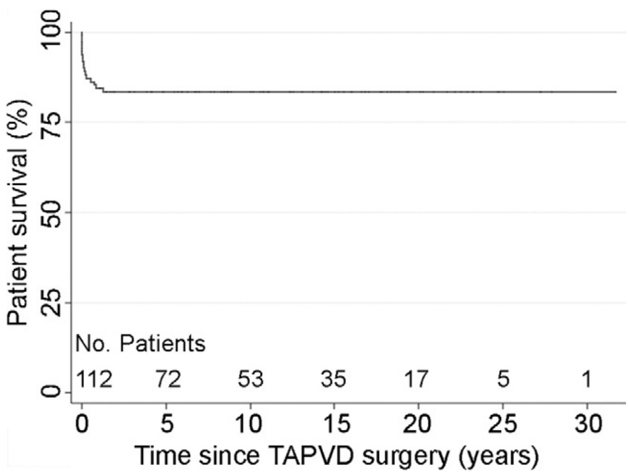

Fig 2. Survival after repair. (TAPVD = total anomalous pulmonary venous drainage.)

TAPVD. Despite improvement of overall perioperative care of patients with congenital heart disease at our hospital over the last decades, this study demonstrated unchanged hospital mortality in neonates with TAPVD surgery. The mortality during the 3 consecutive time periods (1973 to 1988, 1989 to 1998, and 1999 to 2008) was 10.5% (4 of 38), 9.8% (4 of 41), and 12.1% (4 of 33), respectively. This may be partly explained by the fact that over the last decade, surgeons operated on sicker patients who would not have received surgery during the earlier years. This is supported by the observation of a higher incidence of severe obstruction in the last 10 years (Table 2). Furthermore, emergent surgery was significantly more common than urgent surgery in the latest era compared with the previous decades. Moreover, in the last 10 years, a higher proportion of patients arrived in the operating theatre with acidosis. There were also significantly fewer interstate patients in the latest era; patients who survived long-distance transport were likely to be more stable and would be expected to have better outcomes than local patients who were in extremis and required emergency surgery.

This study demonstrated 2 independent risk factors for hospital mortality. Prolonged CPB time (>65 minutes) was a significant risk factor for early death. Prolonged CPB is likely a reflection of greater intraoperative difficulties. Several authors [13, 15, 16] have reported that the urgency of surgery is no longer a risk factor for hospital mortality. In contrast, the recent study by Karamlou and colleagues [6] in 2007 found younger age at repair to be a risk factor for mortality and suggested that younger age was a surrogate for more emergent repair in neonates with severely obstructed TAPVD. Thus, the findings of Karamlou and colleagues appear to be consistent with our observation that severe obstruction of pulmonary venous return (ie, emergent-urgent surgery) remains a risk factor for hospital mortality in neonatal TAPVD surgery. Hence, this was an important finding that suggested the technical capabilities in managing these severely obstructed TAPVD neonates might have reached its limits. A better understanding of mechanisms and management of pulmonary hypertension after repair of neonatal TAPVD is required. Stenting of the obstructed vertical vein to forestall emergent surgery has been described in the literature, [9, 17] and may be a useful adjunct in carefully selected patients [6, 9, 17]. However, stenting has not been used in our institution.

Late Mortality

In this study, reoperation for PVO distant from the site of anastomosis occurred soon after primary surgery and was associated with high mortality (55.6%, 5 of 9). These findings are consistent with the literature [6, 15, 18, 19]. In contrast, anastomotic strictures developed with no deaths in patients requiring reoperation. This suggested, as the literature reports, a better outcome in this subset of patients [15, 20].

A postoperative episode of pulmonary hypertensive crisis was a predictor of late mortality in this study. Similarly, Bando and colleagues [4] reported a higher risk of late mortality in patients after a postoperative episode of pulmonary hypertensive crisis or persistent pulmonary hypertension. It has been suggested that various physiological alterations may cause vasoconstriction of the fibrotic and hypertrophied pulmonary vessels found in TAPVD patients [3]. We speculate that the occurrence of an episode of pulmonary hypertensive crisis was an indication of severe structural abnormalities in the lung vasculature [21]. Furthermore, in some patients there may have been underlying low-grade obstruction (microobstruction) that was not amenable to surgery [18, 22]. Late death as a result of pulmonary hypertension without any obvious recurrent PVO has also been reported in the literature [4, 23].

Low operative weight (≤2.5kg) was found to be a risk factor for late death on multivariable analysis, and is not currently reported by other studies. This finding suggests that smaller neonates represented a greater intraopera-

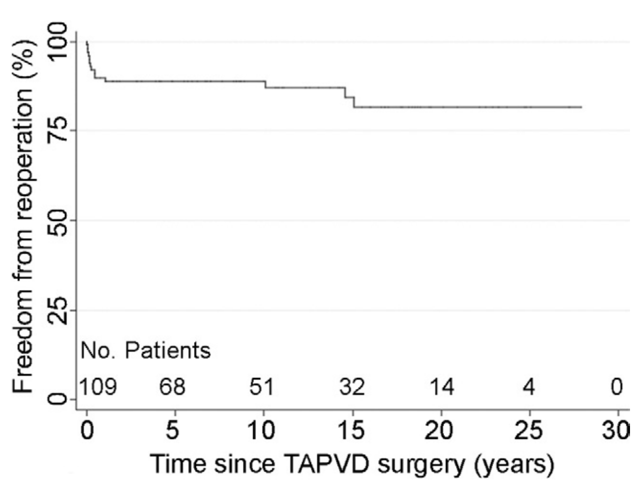

Fig 3. Freedom from reoperation for recurrent pulmonary venous obstruction. (TAPVD = total anomalous pulmonary venous drainage.)

tive challenge to surgeons. The surgical difficulty may have led to trauma and subsequent development of micro-obstruction in the pulmonary veins. Micro-obstructions, with recurrent PVO not detectable by conventional cardiac imaging, may have been the cause of respiratory issues in 33.3% (2 of 6) of late deaths in our study, which is similar to the observations of others [4, 23]. Further research into the postoperative management of micro-obstruction is required.

The lung pathology found in this study is documented in the literature [4, 24, 25]. The subset of TAPVD patients who have lymphatic congestion have poor prognosis [7, 24]. Risk stratification and further research into this challenging subgroup of patients might be beneficial in the future.

Reoperation for Pulmonary Venous Obstruction

Reoperation for PVO after primary repair was performed in 13 patients (11.9%). So far, we have found no study reporting the incidence of reoperation for PVO after TAPVD surgery in the neonatal period. In our study, multivariable Cox proportional hazards analysis found the following predictors of reoperation for PVO: operative weight less than or equal to 2.5 kg and at least 1 postoperative episode of pulmonary hypertensive crisis. Similarly, Bando and colleagues [4] reported that one of the risks for reoperation, by multivariable logistic analysis, was episodes of postoperative pulmonary hypertensive crisis. As previously mentioned, the occurrence of pulmonary hypertensive crisis postoperatively may reflect intrinsic hypertrophy and fibrosis of the pulmonary vessels [3]. Pulmonary hypertensive crisis could be an early indication of an undetected level of micro-obstruction that may ultimately progress and require reoperation [18, 22]. Lacour-Gayet [26] noted low operative weight less than 2.5 kg was a risk factor for recurrent PVO. Operative weight less than or equal to 2.5 kg was found in this current study to be a significant hazard predictive of reoperation for PVO. This finding suggests that the smaller neonates presented to surgeons a greater intraoperative challenge that may have led to handling of the pulmonary veins. Neonatal venous tissue is fragile [26] and handling may develop into recurrent PVO. Lacour-Gayet suggested a "no touch" technique that entails circulatory arrest, minimal dissection, and minimal incision of the pulmonary veins. A decrease in recurrence of PVO after implementation of this technique has been reported [26–28]. Application of the "no touch" technique may be of benefit in neonatal TAPVD surgery, if properly used [26–28].

Functional Status

Of the 90 survivors with follow-up at the end of the series, 95.6% (86 of 90) were either in NYHA class I or class II. Other long-term studies have observed similar findings [4, 29]. This was an encouraging observation as survival beyond 2 years after TAPVD surgery offered good outcomes, at least until early adulthood.

Limitations

The study is subject to the usual limitations of a retrospective review. Cardiac imaging techniques varied during the study period. Patient selection was unlikely to have been uniform throughout and the latest surgical era included patients who were sicker preoperatively. Histologic examination of the lungs was confined to patients who died and it is therefore unclear to what extent it is representative of all neonates undergoing TAPVD repair.

Conclusions

We have determined outcomes associated with TAPVD repair during the neonatal period. Mortality remained unchanged in a large volume single institution over the 36-year period. Risk factors for hospital mortality were urgency of surgery and CPB time greater than 65 minutes, while those for late mortality were low operative weight and postoperative episode of pulmonary hypertensive crisis. Further reduction in mortality will likely require development of effective medical management for patients who have peripheral pulmonary venous obstruction not amenable to surgical repair. Survival beyond 2 years offers excellent outcome.

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Appendix: Variables Analyzed

Patient Characteristics	Sex
	Age at operation
	Weight at surgery (kg)
	Length at surgery (cm)
	Body surface area (m^2)
	Prematurity
	Preoperative acidosis
	Preoperative cardiac arrest
	Preoperative intubation
	Balloon atrial septostomy
Morphology	Anatomical type
	Preoperative obstruction
	Atrial septal defect
	Patent ductus arteriosus
	Ventricular septal defect
	Bilateral superior vena cava
	Noncardiac anomalies
Perfusion Data	Cardiopulmonary bypass time (minutes)
	Circulatory arrest time (min)
	Aortic cross-clamp time (min)
	Minimum temperature (°C)
Procedure	Urgency of surgery
	Vertical vein ligation
Postoperative	Pulmonary hypertensive crisis
	Peritoneal dialysis
	Other cardiac operations during hospital stay