Outcomes of total anomalous pulmonary venous drainage repair in neonates and the impact of pulmonary hypertension on survival.

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Outcomes of simple total anomalous pulmonary venous drainage repair in neonates

Methods:
- Retrospective single center study
- 175 neonates underwent simple TAPVD repair

Results:
Survival
- 86.5% (95%CI 80.3–90.8) at 1 year
- 85.8% (95%CI 79.6–90.3%) at 5, 10, 15 and 20 years

Risk factors for mortality
- PHT crisis (HR 4.93, 95%CI 1.95–12.51, \( P=0.001 \))
- Urgency of surgery (HR 2.51, 95%CI 1.11–5.68, \( P=0.027 \))
- Higher postoperative pulmonary artery to systemic blood pressure ratio (HR 329, 95%CI 293–392, \( P=0.026 \))

Histopathology of lung tissue
- Performed in 17 patients
- Signs of pulmonary arterial hypertension with media hypertrophy in 58.8%

Conclusions:
- Mortality after TAPVD repair occurred mainly within the first year of life
- Pulmonary arterial hypertension seems to be a risk factor for mortality
- Lung biopsy could help to identify patients with evolving pulmonary arterial hypertension and guide new treatment modalities to improve survival
Outcomes of total anomalous pulmonary venous drainage repair in neonates and the impact of pulmonary hypertension on survival.

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Abbreviations

CCT – cross-clamp time
CI - confidence interval
CPB – cardiopulmonary bypass
CVP – central venous pressure
HR - hazard ratio
ICU – intensive care unit
IQR - interquartile range
MAP – mean systemic arterial pressure
PAP – mean pulmonary arterial pressure
PHT – pulmonary hypertension
PVO – pulmonary venous obstruction
SD – standard deviation
TAPVD – total anomalous pulmonary venous drainage
Central picture legend

Lung tissue of obstructed TAPVD with severe media hypertrophy of the pulmonary artery (*).

Central message

Mortality after neonatal TAPVD repair has not improved over time. Identification of patients with pulmonary artery disease could help to guide treatment strategies and potentially improve outcomes.

Perspective statement

Long-term survival after neonatal TAPVD repair was excellent. Mortality occurred mainly within the first year of life. Urgency of surgery, pulmonary hypertensive crisis and higher ratio of pulmonary artery to systemic blood pressure were risk factors for mortality. Lung biopsy could help to identify patients with evolving pulmonary arterial hypertension and guide new treatment modalities.
Abstract

Objective: Mortality after total anomalous pulmonary venous drainage (TAPVD) repair in neonates has remained high. Analysis of risk factors may help to identify therapeutic targets to improve survival.

Methods: Retrospective analysis of all neonates who underwent simple TAPVD repair.

Results: From 1973-2021, 175 neonates underwent TAPVD repair at a median age of 6 days (IQR 2-15) and mean weight of 3.2±0.6 kg. TAPVD was supracardiac in 42.3% (74/175), cardiac in 14.3% (25/175), infracardiac in 40% (70/175) and mixed type in 3.4% (6/175) with obstruction in 65.7% (115/175). Pulmonary hypertensive (PHT) crisis occurred in 12% (21/175). Early mortality was 9.7% (17/175) and late mortality 5.1% (8/158) of which most occurred within 1 year (75%, 6/8). Survival was 86.5% (95%CI 80.3-90.8) at 1 year and 85.8% (95%CI 79.6-90.3%) at 5, 10, 15 and 20 years, respectively. Survival was lower in patients with obstructed TAPVD, with emergent surgery and those with PHT crisis. PHT crisis (HR 4.93, 95%CI 1.95-12.51, P=0.001), urgency of surgery (HR 2.51, 95%CI 1.11-5.68, P=0.027) and higher pulmonary artery to systemic blood pressure ratio (HR 329, 95%CI 2-53290, P=0.026) were risk factors for mortality. Histopathological analysis of 17 patients (9.7%, 17/175) showed signs of pulmonary arterial hypertension with media hypertrophy in 58.8% (10/17).

Conclusion: Mortality after TAPVD repair occurred mainly within the first year of life. Pulmonary hypertension seems to be a risk factor for mortality. Lung biopsy might be useful to identify patients at risk and guide newer treatment modalities.

Keywords: TAPVD, TAPVC, TAPVR, total anomalous pulmonary venous connection, neonatal repair, pulmonary arterial hypertension
Introduction

Many diagnostic and therapeutic advancements have led to increasingly better outcomes after surgery for most congenital heart defects in the past decades. Although outcomes have improved for patients with total anomalous pulmonary venous drainage (TAPVD) as well, mortality has still remained at 9-30%[1–10]. Especially in patients who require repair at neonatal age, a lack of improvement in outcomes has been observed[5]. Evolution in repair techniques towards reduced handling of the pulmonary veins and the use of primary pericardial anastomosis have reduced the rate of recurrent pulmonary venous obstruction and lowered reoperation rates, however neonates remain at risk with substantial mortality[5,11–14]. If operative and perioperative refinements have not significantly improved neonatal survival, this may indicate that intrinsic patient’s characteristics influence outcomes. Therefore, an analysis of risk factors could help to find potential treatment targets to improve survival in these patients.

The aim of this study was to determine the outcomes of simple TAPVD repair in neonates over a timespan of almost 50 years and to identify risk factors for mortality. In particular, we investigated whether pulmonary hypertension could affect survival of these patients.

Methods

Study design

This single-institution retrospective study was approved by the institutional human research ethics committee (HREC number 42425, 14/08/2017) with waived need for informed written consent. All patients were included who underwent TAPVD repair within first month of life between 1973 and 2021. Patients with single ventricle anatomy or additional complex cardiac procedures were excluded. Data was collected retrospectively from the hospital records either as paper chart or digital record. If available, postoperative hemodynamic data were recorded
hourly for the first 36 hours after surgery and included average mean systemic arterial pressure (MAP), mean pulmonary artery pressure (PAP) and central venous pressure (CVP).

Survival and risk factors for mortality were analyzed. For patients with hemodynamic data available, the ratio of PAP/MAP was calculated for each hour. The highest ratio at any time was used to calculate the hemodynamic index ((PAP/MAP)/weight).

Follow-up was obtained from correspondence with cardiologists and general practitioners.

**Definitions**

Emergent surgery was defined as life-saving surgery in a hemodynamically unstable patient within the first 24 hours of diagnosis, urgent surgery as procedure occurring within 24 to 48 hours of diagnosis in hemodynamically stable patients. All other patients were classified as non-urgent. Prematurity was defined as birth at less than 37 weeks of gestation. Pulmonary venous obstruction was determined clinically and by echocardiogram. Obstructed TAPVD was defined as any restriction in pulmonary venous drainage at any level. Postoperative pulmonary hypertensive crisis was recorded by staff when there was acute rise in pulmonary arterial pressure accompanied by an apparent reduction in cardiac output as noted with a significant drop in systemic arterial pressure or when there was strong clinical suspicion due to acute drop in systemic arterial pressure with high central venous pressure and decreased lung compliance in those patients without a pulmonary arterial line. The hemodynamic index (HI) was defined as:

\[
HI = \frac{(PAP/MAP)}{\text{operative weight}} \quad [15].
\]

Acute kidney injury was defined as increase in serum creatinine levels >50% from preoperative baseline. Early mortality was defined as death within 30 days after surgery or before discharge from the hospital, late mortality as death beyond 30 days after surgery and after hospital discharge.

**Operative technique**
The procedures were performed with varying degrees of hypothermia (18°C - 32°C) and blood cardioplegia was used for cardiac arrest. Periods of circulatory arrest were used if needed. Repair was either done by side-to-side anastomosis between the pulmonary venous confluence and the left atrium or primary sutureless technique by fashioning a pericardial anastomosis[16].

**Statistical analysis**

Descriptive statistics include mean ± standard deviation for normal continuous data, median with interquartile range (IQR) for skewed continuous data and frequency with percentage for categorical data. The t-test was used to compare normally distributed continuous variables and the Mann-Whitney U test to compare not normally distributed continuous variables between groups. The chi-square test and Fisher exact test were used to compare categorical data.

The distributions of survival and freedom from reoperation were estimated using Kaplan-Meier methodology. Distributions of time-to-event by selected patient groups were compared using the log-rank test. Cox proportional hazard modeling was used to determine risk factors for mortality and reoperation. Risk factors with a $P$ value less than 0.1 on univariable analysis were included in a multivariable analysis.

Statistical significance was set at $P < 0.05$ and confidence intervals (CI) at 95%. Data analysis was performed with Stata version 17 (StataCorp, College Station, Texas, USA).

**Results**

**Patient and procedure characteristics**

Between 1973 and 2021, 175 neonates underwent simple TAPVD repair (Table 1) including 10.3% (18/175) born prematurely. Anomalous drainage was supracardiac in 42.3% (74/175), cardiac in 14.3% (25/175), infracardiac in 40% (70/175) and mixed type in 3.4% (6/175). Obstruction occurred in 65.7% (115/175) of patients. Preoperative mechanical ventilation was required in 64.6% (113/175) and extracorporeal membrane oxygenation (ECMO) in 4%
(7/175). Indications for early repair of cardiac TAPVD were either obstructed drainage (36%, 9/25) or heart failure despite medical treatment (64%, 16/25).

Median age at surgery was 6 days (IQR 2-15) and mean weight was 3.2 ± 0.6 kg. Emergent surgery was necessary in 28% (49/175) and urgent surgery in 42.9% (75/175). Repair for supracardiac and infracardiac TAPVD was done by direct anastomosis in 86.1% (124/144) and by pericardial repair in 13.9% (20/144, 13 infracardiac and 7 supracardiac TAPVD). Median cardiopulmonary bypass (CPB) and cross clamp times were 78 min (IQR 53-111) and 39 min (IQR 33-52), respectively. Circulatory arrest was used in 44% (77/175) with a mean duration of 31 ± 12 min. Postoperative ECMO was needed in 7.4% (13/175). The chest was electively left open in 22.3% (39/175). Postoperative pulmonary hypertensive (PHT) crisis occurred in 12% (21/175) and 3.4% had a cardiac arrest (6/175). Acute kidney injury developed in 23.4% (41/175). Median ventilation time was 87 hours (IQR 48-137), median ICU stay 124 hours (IQR 73-182) and median hospital stay 14 days (IQR 10-22).

**Survival**

The median follow-up time was 9 years (IQR 1.4-20.4). Early mortality was 9.7% (17/175) and late mortality 5.1% (8/158). Late mortality was due to cardiopulmonary cause in 87.5% (7/8) of which most occurred within 1 year (85.7%, 6/7). There were only two deaths beyond one year after surgery: one patient died 1.3 years after surgery of heart failure in context of progressive pulmonary hypertension and one patient died from a brain tumor 23.6 years after TAPVD repair.

Estimated survival for the entire cohort was 86.5% (95%CI 80.3-90.8) at 1 year and 85.8% (95%CI 79.6-90.3%) at 5, 10, 15 and 20 years, without significant changes over time (**Figure 1A**). Survival was significantly lower in patients with obstructed pulmonary venous drainage with 81.3% (95%CI 72.8-87.4%) at 1 year and 80.4% (95%CI 71.8-86.6%) at 5, 10, 15 and 20 years (**Figure 1B**) and even worse in patient who required emergent surgery with a survival of...
71.4% (95%CI 56.6-82) at 1 year and 69.3% (95%CI 54.4-80.2%) at 5, 10, 15 and 20 years, respectively (Figure 1C). Mortality was highest in patients with recorded postoperative pulmonary hypertensive (PHT) crisis who had a survival of 57.1% (95%CI 33.8-74.9) at 1, 5, 10, 15 and 20 years (Figure 1D). There were no differences in survival between TAPVD types (log-rank \(P=0.53\)).

On multivariable analysis PHT crisis (HR 4.93, 95%CI 1.95-12.51, \(P=0.001\)) and urgency of the procedure (HR 2.51, 95%CI 1.11-5.68, \(P=0.027\)) were identified as risk factors for mortality (Table 2, Figure 2).

Postoperative hemodynamic data

Postoperative PAP was not measured in patients operated before 1994 (n=58). Between 1994 and 2021, 117 patients were treated and postoperative PAP was measured with a pulmonary arterial line in 92 patients (78.6%, 92/117). Of these, 11 patients (12%, 11/92) were on postoperative ECMO support and were therefore excluded from the hemodynamic analysis. Hourly PAP/MAP ratio and hemodynamic index were calculated. Hemodynamic data during the first 36 hours after surgery are displayed in Table 3. There were 7 deaths (8.6%, 7/81) in this subgroup of patients. Patients who died had a higher average PAP with 27.2 (IQR 20.4-28) mmHg (\(P=0.046\)), higher PAP/MAP ratios (\(P=0.02\)) and hemodynamic indices (\(P=0.04\)) compared to patients who survived. Higher average PAP/MAP ratio (HR 329, 95%CI 2-53290, \(P=0.026\)) was identified as risk factor for mortality.

Pulmonary histopathology

A lung biopsy was performed in 9 patients (5.1%, 9/175) of whom 6 patients required ECMO support (66.7%, 6/9) and 6 patients (66.7%, 6/9) died eventually. Further 8 patients underwent post mortem inspection of their lung tissue as part of an autopsy. For all patients with lung tissue available for examination (9.7%, 17/175) the histopathological analysis showed signs of pulmonary hypertension with media hypertrophy in 58.8% (10/17), lymphangiectasia in 52.9%
(9/17) and thickened pulmonary veins in 5.9% (1/17). Three patients (17.6%, 3/17) had either normal histology or only mild changes.

**Figure 3** exemplifies the histopathological findings of three consecutive neonates who underwent simple TAPVD repair: Patient 1 had unobstructed supracardiac TAPVD with non-urgent repair and the pulmonary tissue demonstrated no pathological changes. Patient 2 had obstructed infracardiac TAPVD and required preoperative intubation and an urgent repair. The biopsy showed mild media hypertrophy consistent with initial changes of pulmonary arterial hypertension (PAH). The veins were unremarkable. The patient was started on PAH medication and had an uneventful recovery. Patient 3 had a severely obstructed supracardiac TAPVD that required emergent surgery with preoperative ECMO cannulation. Lung biopsy demonstrated severe media hypertrophy of the pulmonary arteries consistent with severe PAH. The veins showed no abnormalities. The clinical status improved remarkably on PAH medication. However, the patient eventually died after 4 months in the hospital from progressively worsening PAH with ongoing PHT crisis despite maximum medical therapy.

**Reoperation for pulmonary vein obstruction**

There were 20 patients (11.4%, 20/175) with recurrent pulmonary vein obstruction either at the anastomosis site (35%, 7/20) or due to stenosis of pulmonary veins (55%, 11/20) or a combination of both (10%, 2/20) who had to undergo reoperation. Median time to reoperation was 5 months (IQR 0.1-1.2 years). Freedom from reoperation was 90.0% (95%CI 85.2-94.5%) at 1 year, 89.5% (95%CI 83.4-93.4%) at 5 years, 88.3% (95%CI 81.8-92.7%) at 10 years, 87.2% (95%CI 80.2-91.9%) at 15 years and 84.1% (95%CI 75.6-89.8%) at 20 years, respectively (**Figure 4A**). There was no significant difference in freedom from reoperation between patients with direct anastomosis (n=124) and pericardial anastomosis (n=20) (log-rank \( P=0.63 \)). However, freedom from PV reoperation was significantly lower in premature neonates (**Figure 4B**). On multivariable analysis, prematurity (HR 4.05, 95%CI 1.07-15.27,
and PHT crisis (HR 4.27, 95%CI 1.25-14.59, \(P=0.02\)) were identified as risk factors for PV reoperation (Table 2). In patients requiring PV reoperation due to pulmonary vein stenosis, prematurity was the only significant risk factor identified (HR 4.59, 95%CI 1.41-14.92, \(P=0.011\)).

Discussion

Total anomalous pulmonary venous drainage requires repair during the neonatal period when patients are symptomatic. Obstruction of the pulmonary venous return has been a known risk factor for mortality, but also for recurrent obstruction with need for reoperation[1,2,8,9,11]. While obstruction can be hard to quantify, symptoms usually dictate the urgency of the repair and there has been a clear association between urgency of the procedure and survival[2,3]. However, this risk factor is difficult to modify. Prenatal diagnosis can facilitate timely treatment, but in the absence of heterotaxy syndrome the diagnosis is frequently only made once the child begins to exhibit symptoms[17]. Therefore, mortality for neonatal TAPVD repair has not changed much despite significant overall outcome improvements[12,13]. The reported survival ranges between 70-91%[1–9]. In our series covering a timespan of almost 50 years, survival was 85.8% and we did not find a significant change in neonatal survival over time. Mortality after the repair occurred either early before hospital discharge or mostly within one year of life. For those patients who survived the first year, long-term survival was excellent. No patient in our series died from a cardiopulmonary cause beyond 16 months which is similar to the reports of other groups[6]. Although, long-term health is good neurodevelopmental difficulties have been reported later in life[18,19].

While patients who presented with obstructed TAPVD had lower survival, multivariable regression showed that the urgency of the procedure and the postoperative occurrence of PHT crisis were risk factors for mortality. Patients with PHT crisis had the lowest survival with
57.1% after one year in our cohort. To better understand the significance of pulmonary vascular disease for mortality, we analyzed the postoperative hemodynamic data of patients who had monitoring of their pulmonary artery pressure after the procedure. While we increasingly placed pulmonary artery lines over the past years, it has not been done consistently for all patients and was not performed in the historic era. We ultimately analyzed hemodynamic data of 81 patients (46.3%, 81/175) after excluding those on ECMO (n=11). This selection certainly resulted in a cohort of patients that was missing some patients at particularly high risk for elevated pulmonary arterial pressure. Nevertheless, we found significantly higher average PAP, PAP/MAP ratios and hemodynamic indices in patients who died compared to those who survived and a higher PAP/MAP ratio was identified as hazard for mortality. However, the underlying cause for a higher postoperative pulmonary artery pressure can be multifactorial. We therefore set out to investigate if disease of the pulmonary vasculature itself might contribute to the inferior outcome in some patients. We reviewed the histopathological reports from lung biopsies as well as from autopsy studies. We found a significant proportion of patients that had media hypertrophy in their pulmonary arteries consistent with pulmonary arterial hypertension, but only one patient with abnormal pulmonary veins. However, we have to emphasize that lung biopsies were only performed in a minority of patients and mainly in those who were clinically not doing well. Therefore, these findings can’t be generalized. Further data is needed to see how many patients are affected by changes in the pulmonary vasculature. In a small series of three consecutive patients, we analyzed pulmonary tissue from biopsies taken at time of repair to look for early changes in the vasculature. In those patients, we found in both patients with obstructed TAPVD that the pulmonary arteries demonstrated mild to severe media hypertrophy suggesting early changes of pulmonary arterial hypertension. This data suggests that some neonates have pulmonary artery disease early in life, which should be con-
sidered particularly in patients with obstructed drainage. Those patients could potentially ben-
et from early pulmonary hypertension treatment once residual pulmonary venous obstruction
has been ruled out and a wide confluence anastomosis has been confirmed. This is particularly
important as postoperative pulmonary venous obstruction itself is a risk factor for mortality
and residual obstruction should be addressed early[20,21]. However, media hypertrophy in the
pulmonary arteries could easily explain the observed beneficial effects of nitric oxide use in
the postoperative course of patients with obstructed TAPVD[10,22]. While it is unclear from
our data how well those patients with pulmonary artery disease respond to medical treatment
and if the changes in the pulmonary vasculature are reversible, this might be a treatment target
to further improve outcomes after neonatal TAPVD repair in the future. Therefore, routine lung
biopsy at time of repair could help to identify patients with early pulmonary artery disease and
trigger timely medical treatment. Further investigations are needed to understand how many
patients are affected by early changes and whether preemptive treatment might be warranted
or not.

Limitations

This study is limited by its retrospective design. The histopathological results came from a
highly selected subset of patients. Biopsy was mostly performed due to failure to progress in
absence of residual obstruction. Furthermore, we included autopsy results from deceased pa-
tients. It is therefore unclear how many patients are affected by those changes and whether
these changes are present from the beginning or develop later. Unfortunately, this study could
not analyze the effects of PAH medication on outcome.

Conclusions

Survival after simple neonatal TAPVD repair did not improve over time. Mortality mainly
occurred within the first year of life, after that long-term survival is excellent. Urgency of
surgery, pulmonary hypertensive crisis and higher ratio of pulmonary artery to systemic
blood pressure were risk factors for mortality. Lung biopsy could help to identify patients with evolving pulmonary arterial hypertension and guide new treatment modalities to improve survival.
References


Domadia S, Kumar SR, Votava-Smith JK, Pruett JD. Neonatal Outcomes in Total


Tables

**Table 1:** Patient characteristics of 175 neonates who underwent simple TAPVD repair.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neonates (n=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>Age, days</td>
<td>6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>3.2 ± 0.6</td>
</tr>
<tr>
<td>TAPVD type</td>
<td></td>
</tr>
<tr>
<td>Supracardiac</td>
<td>74 (42.3%)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>25 (14.3%)</td>
</tr>
<tr>
<td>Infracardiac</td>
<td>70 (40%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>6 (3.4%)</td>
</tr>
<tr>
<td>Prematurity</td>
<td>18 (10.3%)</td>
</tr>
<tr>
<td>Urgency</td>
<td></td>
</tr>
<tr>
<td>Emergent</td>
<td>49 (28%)</td>
</tr>
<tr>
<td>Urgent</td>
<td>75 (42.9%)</td>
</tr>
<tr>
<td>Non-urgent</td>
<td>51 (29.1%)</td>
</tr>
<tr>
<td>PHT crisis</td>
<td>21 (12%)</td>
</tr>
<tr>
<td>Postoperative ECMO</td>
<td>13 (7.4%)</td>
</tr>
</tbody>
</table>

Values are n (%) or median (interquartile range).

IQR - interquartile range.

**Table 2:** Uni- and multivariable Cox model for mortality and pulmonary vein reoperation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mortality Univariable</th>
<th>Multivariable</th>
<th>Reoperation Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Age at surgery</td>
<td>0.036</td>
<td>0.96 (0.91-1.02)</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Prematurity</td>
<td>0.004</td>
<td>1.65 (0.44-6.25)</td>
<td>0.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight &lt;2.5 kg</td>
<td>0.004</td>
<td>3.02 (0.93-9.81)</td>
<td>0.07</td>
<td>0.02</td>
</tr>
<tr>
<td>Obstruction</td>
<td>0.012</td>
<td>0.97 (0.16-5.93)</td>
<td>0.98</td>
<td>0.01</td>
</tr>
<tr>
<td>Urgency</td>
<td>&lt;0.001</td>
<td>2.57 (1.13-5.84)</td>
<td>0.02</td>
<td>0.96</td>
</tr>
<tr>
<td>CPB time</td>
<td>0.06</td>
<td>1.01 (0.99-1.01)</td>
<td>0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>Cross-clamp time</td>
<td>0.245</td>
<td>1.0 (0.98-1.04)</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>PHT crisis</td>
<td>&lt;0.001</td>
<td>4.82 (1.91-12.15)</td>
<td>0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>PV reoperation</td>
<td>0.056</td>
<td>1.61 (0.57-4.45)</td>
<td>0.37</td>
<td></td>
</tr>
</tbody>
</table>

CI - confidence interval, CPB - cardiopulmonary bypass, HR - hazard ratio, PHT - pulmonary hypertension, PV - pulmonary vein.
Table 3: Postoperative hemodynamic data for the first 36 hours after surgery comparing patients who survived (n=74) and patients who died (n=7).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (n=74)</th>
<th>Deceased (n=7)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAP (mmHg)</td>
<td>20.6 (18.1-24.6)</td>
<td>27.2 (20.4-28)</td>
<td>0.046</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>49.8 (46.3-52.7)</td>
<td>46.8 (44-47.4)</td>
<td>0.13</td>
</tr>
<tr>
<td>CVP</td>
<td>7.1 (6.2-8.2)</td>
<td>6.6 (5.2-7.7)</td>
<td>0.55</td>
</tr>
<tr>
<td>PAP/MAP</td>
<td>0.42 (0.36-0.49)</td>
<td>0.6 (0.43-0.73)</td>
<td>0.02</td>
</tr>
<tr>
<td>HI</td>
<td>0.2 (0.15-0.26)</td>
<td>0.28 (0.21-0.78)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Values are median (IQR). MAP - mean systemic arterial pressure, PAP - mean pulmonary artery pressure, HI - hemodynamic index.

Figure legend

Figure 1: Kaplan-Meier curves comparing estimated survival over the years (A), patients with and without obstructed pulmonary venous drainage (B), emergent, urgent and non-urgent repairs (C) and patients with and without postoperative pulmonary hypertensive (PHT) crisis. Shaded areas represent 95% confidence bands.

Figure 2: Outcome analysis of 175 neonates who underwent simple total anomalous pulmonary venous drainage repair identified pulmonary hypertensive crisis, urgency of surgery and higher postoperative pulmonary artery to systemic blood pressure as risk factors for mortality. A significant proportion of patients with lung tissue available for analysis (n=17) showed signs of pulmonary arterial hypertension.

Figure 3: Pulmonary tissue of three consecutive patients with hematoxylin and eosin staining. Panel A shows bronchiole and pulmonary artery and panel B the pulmonary veins for each patient.

Patient 1: Normal histology in a patient with unobstructed supracardiac TAPVD and non-urgent repair. Patient 2: Panel A shows mild media hypertrophy in the artery while panel B
demonstrates normal vein histology. This patient had an obstructed infracardiac TAPVD requiring preoperative intubation and urgent repair. **Patient 3:** Panel A demonstrates severe media hypertrophy in the artery resulting in an almost obliterated vessel lumen. Panel B shows no abnormalities in the vein. This patient had a severely obstructed supracardiac TAPVD that required emergent surgery with preoperative cannulation for extracorporeal membrane oxygenation.

**Figure 4:** Kaplan-Meier estimated freedom from pulmonary vein (PV) reoperation for all neonates (A) and comparing patients born prematurely and born at term (B). Shaded areas represent 95% confidence bands.
Outcomes of simple total anomalous pulmonary venous drainage repair in neonates

Methods:
- Retrospective single center study
- 175 neonates underwent simple TAPVD repair

Results:
Survival
- 86.5% (95%CI 80.3–90.8) at 1 year
- 85.8% (95%CI 79.6–90.3%) at 5, 10, 15 and 20 years
Risk factors for mortality
- PHT crisis (HR 4.93, 95%CI 1.95–12.51, P=0.001)
- Urgency of surgery (HR 2.51, 95%CI 1.11–5.68, P=0.027)
- Higher postoperative pulmonary artery to systemic blood pressure ratio (HR 329, 95%CI 2–53290, P=0.026)

Histopathology of lung tissue
- Performed in 17 patients
- Signs of pulmonary arterial hypertension with media hypertrophy in 58.8%

Conclusions:
- Mortality after TAPVD repair occurred mainly within the first year of life
- Pulmonary arterial hypertension seems to be a risk factor for mortality
- Lung biopsy could help to identify patients with evolving pulmonary arterial hypertension and guide new treatment modalities to improve survival
Patient 1

Patient 2

Patient 3

B – bronchiole, A – artery, V – vein