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Risk Factors of Total Anomalous Pulmonary Venous Connection Surgery

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Abstract

Background: Total anomalous pulmonary venous connection is a rare congenital heart disease that needs to be surgically corrected. In our study, we retrospectively evaluated the factors associated with mortality and morbidity in patients undergoing total anomalous pulmonary venous connection surgery.

Patients and methods: Retrospective data were collected on 34 patients with isolated total anomalous pulmonary venous connection seen from 1990 to 2015. The median age at time of repair was 36 days (range, 1 to 2520 days) with median weight of 3.465 kg (range, 1.4 to 20.7 kg). Pulmonary venous obstruction, reintervention, associated factors for mortality and overall mortality were recorded and analyzed.

Results: There were 16 deaths (13 surgical deaths and 3 late deaths due to pulmonary venous restenosis and reintervention). Preoperative pulmonary venous obstruction was presented in 21 patients (21/34, 61.8%) and was found to be associated with overall mortality (p=0.0052). Postoperative pulmonary venous restenosis was also a significant risk factor for mortality (p=0.0421). Emergent surgery is a risk factor for mortality (p=0.004). The associated risk factors, such as pre-operation ventilator FiO_2, pre-operation inotropic use, post-operation ventilator FiO_2 and post-operation epinephrine use were also associated with patient mortality. The initial SpO_2 when arriving at our hospital was a protective factor for mortality.

Conclusion: The overall mortality of total anomalous pulmonary venous connection patients has improved in recent years. However, preoperative pulmonary venous obstruction was still an important risk factor for mortality. Postoperative pulmonary venous restenosis was also a risk factor for mortality. Heart failure and emergent surgery were associated with higher mortality rates.

Keywords: Outcome; Pulmonary venous obstruction; Risk factors; Surgery; Total anomalous pulmonary venous connection

Abbreviations:

ACC: Aortic Cross-Clamp; CPB: Cardiopulmonary Bypass; OP: Operation; PAH: Pulmonary Artery Hypertension; PV: Pulmonary Vein; PVO: Pulmonary Venous Obstruction; TAPVC: Total Anomalous Pulmonary Venous Connection

Introduction

Total anomalous pulmonary venous connection (TAPVC) is a rare congenital heart disease that occurs in only 1% to 3% of children with congenital cardiac anomaly [1,2]. After birth, these patients usually develop progressive pulmonary congestion and heart failure sign due to pulmonary venous return flow obstruction and inadequate cardiac output [3]. Surgical correction is needed after correct diagnosis. Without surgical correction, the prognosis is extremely poor, with a mortality of 80% during infancy [3,4]. In several previous studies, there were many different risk factors for the mortality of TAPVC patients. In light of the variability in risk factors, retrospective evaluation of all patients undergoing repair at National Cheng Kung University Hospital from 1990 to 2015 was done. The purpose of our study was to identify the possible risk factors associated with increased mortality and morbidity.

Materials and Methods

Patients

All patients with a diagnosis of TAPVC were identified from the database of National Cheng Kung University Hospital during 1990 to 2015. Only cases of isolated TAPVC were enrolled. Those with minor associated defects such as atrial septal defect and/or a patent ductus arteriosus were included. However, patients with important concomitant cardiac defects, including single ventricle, atrial isomerism, transposition of the great vessels, and/or hypoplastic left ventricle, were excluded from our study. Only patients who underwent surgical repair and follow-up at our hospital were included. The diagnosis was made by echocardiogram, cardiac catheterization or both. The echocardiographic or catheterization values were extracted from diagnostic reports.

PVO was considered present if Doppler examination measured a pressure gradient along anywhere the vessel of pulmonary venous flow >5 mmHg. Surgical mortality was defined as death within 30 days of surgery or during primary hospitalization. Reintervention was defined as any operation performed secondary to recurrent pulmonary venous obstruction. Demographic and morphological characteristics at initial presentation are shown in **Table 1**. Data were abstracted by the review of clinical records and diagnostic reports obtained from the time of the initial admission to the last available follow-up. Median follow-up time was 3.38 years (minimum, 1 days; maximum 20 years) from repair, with 15 having >1 year of follow-up, and was available for 18 survivors.

Table 1 Demographic and morphological characteristics of patients.

Variable	Value
Age at surgery, median (minimum, maximum)	36 d (1 d, 6y11m/o)
Gender	12 (35.3%)
Female	22 (64.7%)
Male	
Body weight at surgery, mean ± SD (kg)	4.19 ± 3.12
median (kg)	3.465
TAPVC type, case number (%)	
Supracardiac	14 (41.2%)
Coronary sinus	14 (41.2%)
Infracardiac	5 (14.7%)
Mixed	1 (2.9%)
Pulmonary venous obstruction, case number (%)	
Supracardiac	10 (71.4%)
Coronary sinus	7 (50%)
Infracardiac	3 (60%)
Mixed	1 (100%)

Potential variables associated with mortality were examined. These included age and weight at time of the initial repair, gender, low body weight for age, anatomic subtype of TAPVC, preoperative evidence of obstruction, need for additional surgical procedures, cardiopulmonary bypass (CPB) times, aortic cross-clamp (ACC) times, hypothermia times, pre-operation(OP) PVO, pre-OP ventilator FiO_2, post-OP ventilator FiO_2, pre-operational inotropic use, post-OP epinephrine use, post-OP restenosis, pre-OP blood gas acidosis, post-operational hospitalization days and ICU days.

Statistical analysis

Chi-square and Fisher's exact tests of association were conducted to differences of categorical variables. Continuous variables for t test that were distributed normally are presented as means **(Figure 1)**. We constructed Kaplan Meier curves for post-operative duration time for pulmonary vein (PV) restenosis **(Figure 2)**, pulmonary vein reintervention **(Figure 3)** and overall survival rate **(Figure 4)**. Differences across categories were assessed using the log-rank test. Significance for two-sided analysis was set at $P<0.05$. Statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 44 patients were diagnosed with TAPVC. Excluding those associated with other major cardiac anomalies and no operation or follow-up in our hospital, 34 patients with isolated TAPVC were enrolled into our study. Of these 34 patients, 22 were male (64.7%); 12 were female (35.3%). Median age at time of surgical repair was 36 days (range, 1 to 2520 days) with median weight 3.465 kg (range, 1.4 to 20.7 kg). As shown in **Table 1**, 14 patients was supracardiac type (14/34, 41.2%), 14 patients presented with coronary sinus type (14/34, 41.2%), 5 patients presented with infracardiac type (5/34, 14.7%), and 1 patient presented with mixed TAPVC (1/34, 2.9%).

The mixed type was a combination of supracardiac and infracardiac types. At the time of presentation, PVO was present in 61.8% (21/34) of patients. Excluding mixed type (due to only one case), the supracardiac type subgroup had highest rate of PVO (10/14, 71.4%), the infracardiac type had second highest rate of PVO (3/5, 60%) and lowest rate in the coronary sinus type (7/14, 50%). Among the 10 patients with PVO in supracardiac type TAPVC, eight had obstruction of the ascending vertical vein and two had obstruction of the left innominate vein. Of the 3 patients with PVO in infracardiac type TAPVC, two had obstruction of the vertical vein and one had obstruction in the intrahepatic vein. Among the seven patients with PVO in coronary sinus type, three had obstructions in ASD; four had obstructions in the vessel connecting the common pulmonary vein to the coronary sinus.

Figure 1 shows the clinical results of the patient seen at our hospital. Of the 38 patients, 4 patients were excluded due to no operation in our hospital or loss to follow-up. Among the remaining 34 patients, 13 patients had surgical mortality after the surgical repair or during the first hospitalization. The overall surgical mortality was 38.2%. There were three patients (14.3% of surgical survivors) who required surgical reintervention for pulmonary venous obstruction after primary repair. However, these patients had surgical reintervention for PVO but all expired after surgery. The survival rate after first surgery was 61.8%. The overall survival rate during follow-up in our study was 52.9%.

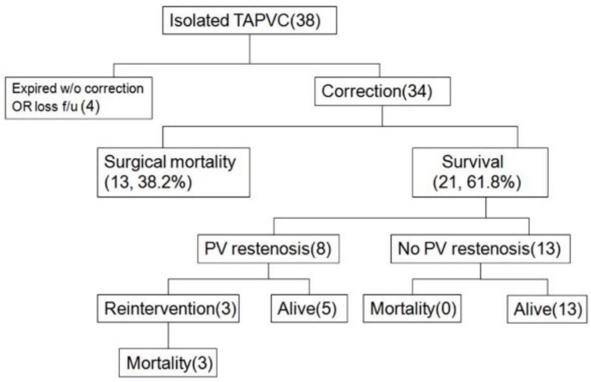

Figure 1 Flow chart of events in patients with isolated TAPVC.

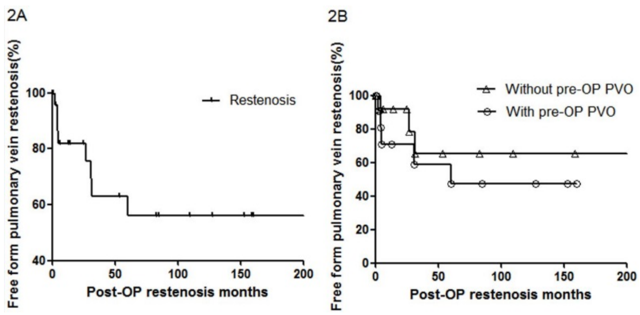

Figure 2 (A) Kaplan-Meier event-free curves to show the rates of free from pulmonary vein restenosis, which were 81.9% at 1 year, 56.1% at 5 years after surgery. **(B)** Kaplan-Meier event-free curves to show the freedom from PV restenosis in patients without (Δ) or with (○) pre-OP PVO.

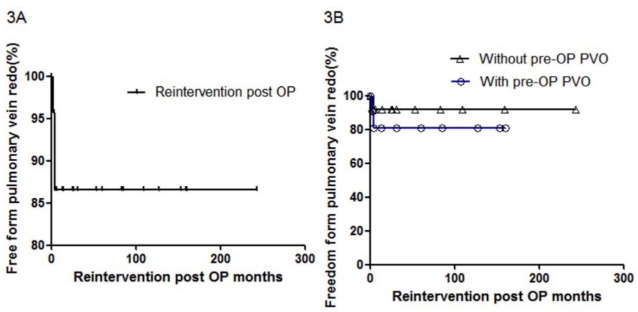

Figure 3 (A) Kaplan-Meier event-free curves to show the rates of freedom from pulmonary vein reintervention, which were 86.6% at 0.5 year and still 86.6% at 1 and 5 years after surgery. **(B)** Kaplan-Meier event-free curves to show the freedom from PV reintervention in patients without (Δ) or with (○) pre-OP PVO.

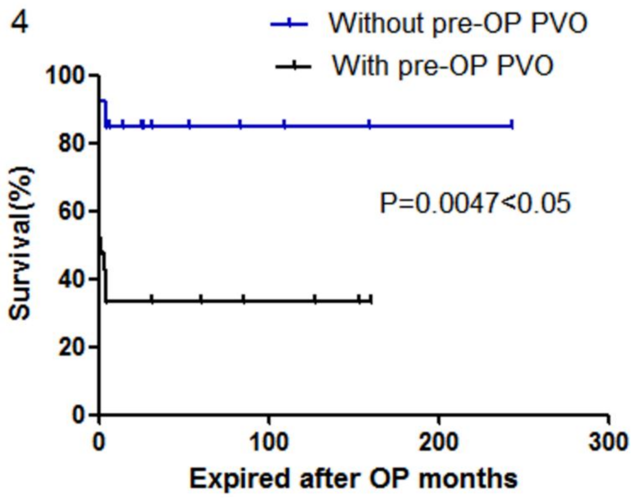

Figure 4 Kaplan-Meier event-free curves to show the overall survival in patients with or without preoperative PVO, with p=0.0047<0.05.

Preoperative pulmonary venous obstruction was noted to be most associated with mortality. The mortality rate was 66.7% in the group with preoperative PVO but 15.3% in the group without preoperative PVO. This finding was statistically significant (p=0.0052, **Table 2**). The surgical mortality was 45.5% (5/11) before 2000 and 21.7% (5/23) after 2000, but no statistically significant difference was noted(p=0.2318).

Simple Cox regression revealed that the preoperative PVO was a significant predictor for the mortality of TAPVC patients (p=0.02, **Table 3**). The overall survival in patients of TAPVC patient without or with preoperative PVO is shown by Kaplan-Meier event-free curves **(Figure 4)**. Patients with preoperative PVO had significantly higher mortality than patients without preoperative PVO (p=0.0047<0.05, **Figure 4**).

PV restenosis was identified in 8 patients (8/21, 38.1%) during follow-up. The freedom from pulmonary vein restenosis was calculated by using the Kaplan-Meier technique. As shown in **Figure 2A**, the freedom from PV restenosis were 81.9%, 56.1% at 1 year, 5 years after first TAPVC correction repair, respectively.

The rates of freedom from PV restenosis decreased rapidly within the five post-operative year and remained stable in the subsequent years. Among patients with PV restenosis, three had symptoms of significant heart failure and required PV surgical reintervention to relieve PV stenosis. These three patients' pulmonary venous flow to LA pressure gradients were 6, 26 and 38.2 mmHg, respectively. The **Figure 2B** show higher rates of freedom from PV restenosis in patients without preoperative PVO, but no significant difference was identified statistically.

Table 2 Characteristics of patients who underwent TAPVC correction.

	Alive	Expired	P value
Number of patients	18	16	
Male/Female	13/5	9/7	0.4754
Age (days), mean	209 ± 581.88	37.63 ± 42	0.2699
Body weight <3% of age, numbers	14	4	0.0051*
Pre-OP PVO, numbers	7	14	0.0052*
Pre-OP blood gas acidosis, numbers	4	6	0.4569
Pre-OP ventilator FiO2 (%), mean	41.22 ± 20.15	77.5 ± 28.6	0.0057*
Pre-OP inotropics use, numbers	7	12	0.0454*
Post-OP ventilator FiO2 (%), mean	51.39 ± 25.43	77.86 ± 23.26	0.005*
Post-OP epinephrine use, number	5	13	0.0026*
Post-OP restenosis	5	3	0.0421*
CPB times (mins), mean	153 ± 52.26	158.46 ± 71.24)	0.8173
ACC times (mins), mean	75 ± 28.58	70.3 ± 21.63	0.6602
Hypothermia times (mins), mean	111.39 ± 40.36	111.43 ± 50.21	0.998
Post-OP ICU days, mean	9.94 ± 5.61	14.87 ± 23.68	0.3985
post-OP hospitalization days, mean	16 ± 7.85	15.87 ± 23.59	0.9821
OP: operation, CPB: cardiopulmonary bypass, ACC: aortic cross clamp, * P<0.05			

Table 3 Simple cox regression analysis, outcome: Mortality.

Parameters	HR	95% CI		P value
Age	0.99	0.98	1.00	0.21
Sex	1.77	0.66	4.77	0.26
Reintervention post OP days	1.01	1.00	1.02	0.30
Pre-OP ventilation days	0.98	0.85	1.13	0.79
Pre-OP ventilation setting (FiO_2)	1.03	1.01	1.05	0.01*
Pre-OP inotropics use	0.26	0.07	0.92	0.04*
Post-OP ventilation days	1.02	0.99	1.04	0.19
Post-OP ventilation setting (FiO_2)	1.03	1.01	1.06	0.005*
Post-OP epinephrine	0.12	0.03	0.54	0.01*
Bypass time	1.00	0.99	1.01	0.91
Hypothermia time	1.00	0.99	1.01	0.77
Aortic clamp time	1.00	0.97	1.02	0.76
Initial gas	0.87	0.02	36.05	0.94
Initial SpO_2	0.93	0.88	0.97	0.002*
Post-OP ICU days	1.00	0.98	1.03	0.76
Post-OP hosp. days	0.99	0.94	1.03	0.50
Pre-OP PVO	0.16	0.04	0.72	0.02*
Post-OP Reintervention	0.52	0.15	1.82	0.30
PV Restenosis	1.83	0.52	6.48	0.35
BW percentile (<3%)	1.19	0.44	3.21	0.73
TAPVC type	0.78	0.19	3.26	0.73
Post-OP infection	1.29	0.37	4.52	0.70
Emergent repair	0.22	0.08	0.62	0.004*
PAH	0.36	0.08	1.58	0.17
*: p<0.05				

The freedom from PV reintervention is shown in **Figure 3A**. Mean number of days to reintervention was 112.3 days. These three patients' PV reintervention procedures were performed within six months after the first surgery. However, these patients all died after PV reintervention.

More than half of the patients (19/34, 55.9%) initially presented with signs of heart failure. Sixteen patients need mechanical ventilation and 19 patients required inotropic support preoperatively. A case review revealed that patients who had obvious signs of heart failure and ventilation or inotropic agent support had a higher mortality rate and more frequently needed emergent repair. After surgical correction, we also found patient who need higher ventilator O_2 and epinephrine support also had higher mortality rate.

When including late mortality within the statistical analysis of investigated variables, we found several statistically significant correlations **(Table 2)**. Besides preoperative pulmonary venous obstruction, these associated risk factors were as follows: pre-OP ventilator FiO_2, pre-OP inotropics use, post-OP ventilator FiO_2, post-OP epinephrine use, post-OP restenosis and emergent repair. Simple cox regression analysis also showed that these associated factors mentioned above were the significant predictor for the mortality of TAPVC patients **(Tables 3 and 4)**.

Discussion

The natural course of TAPVC without surgical treatment is frequently progressive heart failure, which is associated with >80% mortality in the first year of life after surgery [3]. Surgical correction is needed after the diagnosis is confirmed. Improvement in surgical technique, early diagnosis and well post-operative patient care have led to improved results of TAPVC correction patient.

The surgical mortality of TAPVC patients decreased from 80% in early series to 5% in recent reports [5,6]. In our series, the surgical mortality decreased from 45.5% before 2000 to 21.7% after 2000. We collected the associated data of these cases to find the possible risk factors for mortality.

There are four types of TAPVC including supracardiac, coronary sinus, infracardiac and mixed type. In our series, supracardiac and coronary sinus type account for about 82% cases. Several studies have analyzed the relationships between mortality and type of TAPVC. In our studies, we find no association between the type of TAPVC and mortality (p=0.73, **Table 3**). But previous associated studies showed no consistent results [7]. The impact of connection type remains controversial [5-8].

Preoperative pulmonary vein obstruction was reported about 20% to 60% of TAPVC patient [1,2]. The preoperative PVO can be diagnosed by echocardiography with fair sensitivity and specificity [9]. In our series, preoperative PVO was present in 61.8% of patients. Supra-cardiac type had the highest rate (71.4%). Preoperative PVO was found to be associated with overall mortality (p =0.02<0.05, by simple Cox regression, **Table 3**).

Previous reports have revealed that preoperative PVO was also a risk factor for mortality and pulmonary vein reintervention [8,10]. However, not all studies revealed the relationship between PVO and overall mortality [1,2]. In our opinion, preoperative PVO is an important risk factor for overall mortality.

Younger age at repair was noted to be a risk factor for mortality of TAPVC patients in a previous study [1,11]. In early report, Wukasch et al. state that surgical treatment should be delayed until at least 6 months of age [12]. However, Lupinetti et al. found that operative treatment can be performed on TAPVC patients in infancy with low mortality [13]. We also noted that age at the time of surgery is not a risk factor for mortality of TAPVC patient (p=0.2699, **Table 2**). In our studies, better outcomes were found among patients who had early surgical correction. However, previous studies showed no consistent results [1,11,12].

In our series, we state that low body weight (<3% for a given age) is a protective factor (p=0.0051<0.05, **Table 2**). Low body weight at repair is not a risk factor for mortality, and such observation has also been described in other reports [4,14,15]. In our series, surgery was performed as soon as possible after diagnosis was confirmed, regardless of body weight and age.

Among the 34 TAPVC correction surgery in our hospital, 13 surgeries were performed under emergent conditions. An operation was classified as emergent if the patient was taken to the operating room within 24 hours after arriving at our hospital due to hemodynamic or ventilation compromise.

In our series, emergent surgery is a risk factor for mortality (p=0.004, **Table 3**). After arriving our hospital, we found most of these patients was unstable and need higher ventilator setting and inotropic agent support. Then, we recorded the associated data and analyzed them. We found higher ventilator FiO_2 and pre-operative inotropic use were risk factors for mortality of TAPVC. We noted that lower initial SpO_2 when arriving at our hospital was also a risk factor for mortality after TAPVC. We put these risk factors to simple Cox regression analysis and noted a significant correlation (p=0.002, **Table 3**). In previous studies, low cardiac output syndrome was also reported as the main causes of early postoperative death [14,16-18].

In conclusion, the patient who needed such support to compensate for heart failure had a higher mortality rate. So, the patient who had obvious heart failure condition before surgery could be the higher risk patient.

After surgical correction, these patients exhibited a wide range of clinical conditions. Some patient needed higher setting of ventilation but some didn't. The patient who need epinephrine support had more critical condition. The use of epinephrine postoperatively is a risk factor for mortality [1]. In our series, we also found that use of epinephrine postoperatively is a risk factor for mortality of TPAVC patient (p=0.0026, **Table 2**). The patient also had higher FiO_2 ventilator settings (p=0.005, **Table 2**). We put these two factors into simple Cox regression analysis and noted a significant correlation (p=0.01 and p=0.005, respectively, **Table 3**).

Pulmonary vein restenosis after repair of TAPVC is a significant risk factor for mortality in previous study [1,19-21]. In our series, there were eight patients with pulmonary vein restenosis after surgical correction. Among these eight patients, three patients need reintervention due to obvious heart failure.

In a previous study, patients who had restenosis later presented with significant heart failure and required reintervention within 6 months post-operatively [13]. These three patients of our study also had pulmonary vein restenosis episodes within six months, and all died after surgical reintervention.

In our study, post-operative pulmonary restenosis is also a significant risk factor for the mortality of TAPVC patients. We analyzed the associated factors by simple Cox regression. The results revealed that post-operative restenosis was also a significant risk factor for mortality (p=0.01, **Table 4**). However, we noted that initial SpO_2 of patients when arriving our hospital is a protective factor. Higher SpO_2 of patient initially had lower rates of post-operative stenosis **(Table 4)**.

Table 4 Simple cox regression analysis, outcome: restenosis.

Parameters	HR	95% CI		P value
Age	0.98	0.95	1	0.09
BW	0.24	0.04	1.28	0.09
Sex	2.24	0.52	9.64	0.28
Expired after OP days	0.99	0.98	1	0.14
Pre-OP ventilation days	0.89	0.68	1.16	0.39
Pre-OP ventilation setting	1	0.97	1.04	0.8
Pre-OP inotropics use	0.82	0.21	3.31	0.78

Post-OP ventilation days	0.98	0.8 8	1.1	0.77
Post-OP ventilation setting	0.98	0.9 4	1.01	0.16
Post-OP epinephrine	1.09	0.2 6	4.63	0.91
Bypass time	1	0.9 9	1.01	1
Hypothermia	0.99	0.9 7	1.01	0.32
Aortic cross clamp time	1	0.9 7	1.03	0.79
Initial SpO_2	0.9	0.8 3	0.98	0.02*
Post-OP ICU days	0.98	0.8 9	1.08	0.69
Post-OP hosp. days	1.01	0.9 5	1.07	0.8
Pre-OP PVO	0.51	0.1 2	2.16	0.36
Reintervention post OP	0	0	0	1
Mortality	0.04	0	0.41	0.01*
BW percentile (<3%)	1.05	0.2 6	4.2	0.95
TAPVC Type	2.1	0.2 3	18.83	0.51
Post-OP infection	3.17	0.3 9	26.06	0.28
Emergent	0.72	0.1 4	3.56	0.68
PAH	1.95	0.4 3	8.82	0.39
*P<0.05				

Study limitation

There were only 34 cases enrolled in our study from 1990 to 2015. Multivariate analysis was limited by small sample size and thus produces a clear limitation of the study power.

Conclusion

Although overall mortality decreased over time in isolated TAPVC patients, there were still a considerable number of mortality cases among this patient population. Overall mortality in our series was 47.1%. Preoperative pulmonary venous obstruction is an obvious risk factor. Besides, TAPVC correction surgery under emergent condition is also an important risk factor. A greater need for ventilator support and inotropic agent use before or after TAPVC correction are considered risk factors in our studies. Patients with obvious heart failure sign may be associated with the risk factors mentioned above. Pulmonary vein restenosis after repair of TAPVC also contribute to higher mortality rate. Low body weight and younger age at repair were not risk factors. However, low body weight was a protective factor. Surgical correction should be done as soon as possible regardless of body weight and age.

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Disclosure

The authors declare no conflicts of interest.

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