Predictors of prolonged mechanical ventilation after cardiopulmonary bypass in infants with congenital heart disease less than 3 months old

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Abstract

Objective: To identify the predictors of prolonged mechanical ventilation (PMV) after cardiopulmonary bypass (CPB) in infants with congenital heart disease (CHD) less than 3 months.

Methods: From June 2017 to May 2020, a total of 165 infants less than 3 months old with CHD admitted to the Children's Hospital of Nanjing Medical University for CPB were enrolled in this study. The following data were collected including gender, age, weight, Risk Adjustment in Congenital Heart Surgery-1 (RACHS-1) score, preoperative levels of thyroid hormones, CPB time, aortic cross-clamping (ACC) time, mechanical ventilation time, ICU mortality and infection. The PMV was defined as the ventilator assisted time > 72h. PMV prediction was assessed by multivariate binary logistic regression analysis.

Results: Compared with non-PMV group, PMV group was younger (44.74 ± 25.27 days vs. 35.44 ± 26.91 days, P= 0.001), and most were newborns (41/93 vs. 10/57, P=0.000), with a higher proportion of RACHS-1 (29/93 vs.6/57, P=0.000) and more cases of infection (47/93 vs. 17/57,P= 0.004).PMV group had significantly lower weight than non-PMV group (3.79 ± 0.83Kg vs. 4.28 ± 1.01Kg, P=0.001). In PMV group, CPB (133.74 ± 89.65 vs. 72.30 ± 44.82, P =0.000) and ACC time (52.02 ± 24.80 vs. 36.98 ± 16.63, P =0.000) were both longer. FT4 and TT4 were higher while FT3, TT3 and TSH were lower in PMV group, but only FT3 (4.99 ± 1.67 vs. 5.29 ± 1.23, P =0.017) and TT3 (1.91 ± 0.59 vs. 1.96 ± 0.49, P =0.050) showed significant differences between PMV group and non-PMV group.

Conclusion: Multiple logistic regression analysis showed that weight, infection, FT3 and CPB time were independent predictors of PMV after CPB in infants with CHD.

Introduction

Congenital heart disease (CHD) is the most common congenital malformation of the fetus, showing an increasing trend yearly [1]. Without intervention, CHD patients will experience significant incidence of mortality. In the past 50 years, modern cardiac surgery has greatly changed the treatment of CHD, and cardiopulmonary bypass (CPB) is often used in patients with complex CHD [2].

Mechanical ventilation (MV) is a common treatment in intensive care for newborn, children or adults [3].Especially for children undergoing surgery for CHD, MV may be extended for different periods after the surgery, while the prolonged mechanical ventilation (PMV) is defined as the ventilator assisted time > 72h [4]. However, PMV after CHD surgery in children is associated with ventilator-associated lung injury, pneumonia, high postoperative morbidity and mortality, as well as increased use of intensive care units (ICUs) and hospital resource [5,6]. Therefore, early postoperative weaning is necessary to reduce complications and improve prognosis.

Given the adverse effects of PMV, it is important to predict PMV for better prevention and management to shorten extubation time. In this retrospective study, we aimed to identify the predictors of PMV in infants with CHD after CPB.

Methods

Patients

This study was a retrospective, single center study and was approved by the hospital medical ethics committee. All operations were performed with the informed consent of the guardians.

A total of 165 infants less than 3 months old with CHD admitted to the Children's Hospital of Nanjing Medical University from June 2017 to May 2020 were enrolled in this study. Patients were excluded if they met the following criteria: (1) older than 3 months; (2) without CPB; (3) with a history of primary thyroid diseases, such as hyperthyroidism, hypothyroidism, and thyroid tumors; (4) with trisomy 21 syndrome.

The demographic data were collected including gender, age, weight, Risk Adjustment in Congenital Heart Surgery-1 (RACHS-1) score [7], type of CHD, CPB time, aortic cross-clamping (ACC) time, infection, MV time, ICU mortality, and preoperative levels of thyroid hormones: total T3 (TT3, normal range: 1.29-3.11 nmol/L), free T3 (FT3, normal range:2.8-7.1 pmol/L), total T4 (TT4, normal range: 66-187.4 nmol/L),free T4(FT4, normal range:12.1-22 pmol/L), thyroid stimulating hormone (TSH, normal range: 0.2-5 μIU/ml).

According to previous experience, the standard of extubation after operation was decided as follows: (1) general principle: if there is no contraindication, extubation should be done as soon as possible, and it can also be extubated the same night after operation. (2) There was no disturbance of internal environment and little drainage fluid (< 1ml/kg.H). (3) Urine volume was satisfactory (> 4 ml/(kg.H). (4) Awake and satisfied, strong spontaneous breathing. (5) The peak pressure of ventilator was less than 16 cmh2o, the volume fraction of inhaled oxygen was less than 400 ml/L, the partial pressure of arterial oxygen was more than 90 mmHg, and the partial pressure of carbon dioxide was about 35 mmhg. (6) For infants with body weight less than 3.5 kg, the operation process was not smooth, and the CPB was more than 50% of the normal value, no extubation was performed on the night after operation. Successful extubation criteria: no intubation within 72 hours after extubation. If intubation is performed within 72 hours after the operation, the follow-up ventilator assistance time will be calculated continuously, if the first extubation is successful, the subsequent ventilator assistance time will not be included. According to the clinical experience, PMV was defined as the ventilator assisted time > 72h [8-10].

Based on mechanical ventilation duration, the cases were divided into two groups: PMV group with no less than 72 hours of mechanical ventilation, and non-PMV with less than 72 hours of mechanical ventilation. In addition, patients in death group were intubated many times after operation, and MV time could be more than 72 hours, or less than 72 hours, but eventually died due to various causes. Considering the possible influence of other factors, such as low birth weight, severe preoperative infection and postoperative low cardiac output syndrome (LCOS), the cases were not included in PMV group or non-PMV group.

Statistical analysis

The statistical analysis was performed with SPSS version 20.0 software (Chicago, IL, USA). Continuous variables were expressed as the mean ± standard deviation, while

categorical variables were expressed as frequencies and percentages. Comparisons between groups were made using unpaired Student's t-test for continuous variables and χ^2 or Fisher's exact test for categorical variables. Multivariate binary logistic regression analysis was performed to assess the independent PMV predictors. $P < 0.05$ was considered to be statistically significant.

Results

Baseline characteristics

A total of 165 infants younger than 3 months (mean age 36.94 ± 26.60 days, 65.5% male) met the inclusion criteria, including 62 newborns (37.6%). Among them, 44 patients (26.7%) scored RACHS-1 ≥ 4. A total of 75 cases (45.5%) were infected, including positive blood culture and sputum culture. 15 patients (9.1%) died in ICU. The median intraoperative CPB time was 114.56±80.38 min, ACC time was 47.94± 23.30 min. Preoperative thyroid hormone range: FT3 (5.00 ± 1.51 pmol /L), FT4 (21.02 ± 5.93 pmol/L), TT3 (1.90 ± 0.55 nmol/L), TT4 (120.23 ± 33.95 nmol/L) and TSH (5.54 ± 5.92 μIU/ml). Except for 15 dead patients, the time of MV was 127.08 ± 126.95 minutes, including the time of reintubation within 72 hours after operation. The demographic characteristics of the included patients are listed in Table 1.

Comparison of PMV group and non-PMV group

Among the 165 patients, there were 15 patients in the death group. There were significant differences in age, gender and FT3 between PMV and non-PMV groups. Compared with non-PMV group, PMV group were younger (44.74±25.27 days vs. 35.44±26.91 days, P= 0.001), and most of them were newborns (41/93 vs. 10/57, P=0.000), with a higher proportion of RACHS-1 (29/93 vs.6/57, P=0.000) and more cases of infection (47/93 vs. 17/57,P= 0.004). PMV group had significantly lower weight than non-PMV group (3.79±0.83 Kg vs. 4.28±1.01 Kg, P=0.001). In PMV group, CPB (133.74±89.65 vs. 72.30±44.82, P =0.000) and ACC time (52.02± 24.80 vs. 36.98±16.63, P =0.000) were both longer. FT4 and TT4 were higher while FT3, TT3 and TSH were lower in PMV group, but only FT3 (4.99±1.67 vs. 5.29± 1.23, P =0.017) and TT3 (1.91±0.59 vs. 1.96±0.49, P =0.050) showed significant differences between PMV group and non-PMV group (Table 2).

Independent predictors of PMV

The predictors with P <0.1 were included in multiple quadratic logistic regression analysis to determine the independent predictors of PMV, except for gender. The risk factors of PMV were weight (P = 0.002), infection (P=0.004), FT3 (P = 0.034), and CPB time (P = 0.008) (Table 3).

Discussion

To our knowledge, this study is the first retrospective analysis of the predictive value of PMV after CPB in patients less than 3 months. In this study, 165 postoperative patients were studied. Multiple logistic regression analysis showed that weight, infection, FT3 and CPB time may be independent predictors of PMV.

It is important to note that most of the included patients were male (108, 65.5%), and all of the death group were male. This may be closely related to Chinese preference for boys over girls. In most of China's rural areas, many families are more willing to raise a boy, so girls can be abandoned after being diagnosed with complex CHD, and do not have a chance to accept the surgical treatment [11,12]. Due to this bias, we excluded gender from multivariate binary logistic regression.

According to previous studies, low body weight is a risk factor for increased mortality [13]. However, this study focused on the correlation between body weight and PMV. Low weight is an important predictor of PMV, the weight is lower in most of the newborn (41,44.1%), these patients are in critical condition and are less likely to to reach normal weight before surgery, on the contrary, if cardiac pathology is complicated by non-cardiac factors, the surgical effect is poor, and PMV and mortality rate are high [14]. Therefore, it is necessary to strengthen nutritional support before and after operation.

The occurrence of infection is also considered as a risk factor for PMV. Infection following cardiac surgery may activate or amplify systemic inflammatory responses triggered by surgery and CPB, thus prolonging the use of ventilators. Careful prevention of associated infections and aggressive anti-infection therapy may contribute to improved ventilator-assisted duration and overall prognosis in all ICU patients.

FT3 is also considered as an important predictor of PMV. Thyroid hormones play an important role in the cardiovascular system, affecting heart function by regulating heart rate, myocardial contractility and systemic vascular resistance. Postoperative thyroid hormone level is considered to be low-cost, complementary prognostic indicator for heart surgery in children with CHD, and the degree of postoperative hypothyroidemia is associated with important clinical endpoints in pediatric cardiac surgery, including duration of mechanical ventilation, intensive care treatment, and degree of muscle support [15,16]. Many children experience a transient decrease in thyroid hormone levels after CPB surgery, which can be recovered by standard treatment measures [17]. It was reported that low serum T3 level after cardiac surgery in children was a predictor of poor prognosis, and T3 treatment can significantly improve cardiac function, which may be the most relevant indicator to evaluate prognosis [18]. Talwar et al. demonstrated that oral T4 improved Cardiac Index (CI) and lowered the demand for muscle strength. In addition, it shortened the MV time, ICU time, total hospitalization time and Therapeutic intervention scoring system (TISS) in children with complicated CHD after surgery [19]. Portman et al. tested the hypothesis that T3 supplements were safe and produced significantly improved postoperative clinical outcomes. They found no difference in extubation time (TTE) and main clinical outcome between the treatment and control groups. However, for children younger than 5 months, randomization to T 3 significantly reduced the

median TTE in the treatment group (55 vs. 98 hours) compared with the placebo group [20]. In our study, FT3 was found to be a predictor of PMV. Therefore, preoperative thyroid hormone level could be used to investigate whether preoperative thyroid hormone level and thyroid hormone supplement could improve the prognosis.

As expected, CPB time was longer in PMV group, with significant significance ($P<0.05$). At present, few studies investigated the relationship between CPB and PMV. Mittnacht et al. [23] found that the risk of early extubation failure in CPB patients lasting more than 150 minutes increased by 11.8 times. Szekly et al. [24] found a correlation between CPB duration and extubation delay. According to Reddy and his colleagues [23], CPB duration and ACC duration were longer for the patients who died. Neither CPB nor ACC time per se is a risk factor for early death, rather it reflects the high complexity of cardiac malformation, which requires more technical repair and prolonged extracorporeal circulation support. Many studies have shown that open-heart surgery can lead to a significant decrease in thyroid hormones [26]. Low levels of T3 or T4 were associated with the incidence of CPB after open heart surgery. Low thyroid hormone levels after surgery may lead to poor prognosis. If CPB is considered to cause thyroid hormone reduction, preoperative thyroid hormone increase can improve the prognosis [27,28].

Simple cardiac surgery can lead to early extubation. It has been reported that early extubation can be achieved even after complex cardiac surgery. Early extubation and withdrawal after CHD can enable patients to recover quickly, improve cardiopulmonary function, and shorten the length of ICU and total hospital stay [27-32]. To solve the problem of delayed extubation, the risk factors before, during and after the operation can be determined to help change the operation or treatment plan and remove the ventilator early [3]. For example, preoperative nutritional support can be increased, nutritional status can be adjusted, and normal preoperative thyroid hormone value can be maintained. In addition, the improvement of MV protocol and early extubation can reduce complications and improve prognosis [35,36]. Therefore, it is necessary to identify clinical predictors of PMV after pediatric cardiac surgery.

Limitations

There are some limitations in our study. First, this study is a retrospective study, which inevitably leads to bias. Second, the sample size of this retrospective study is small. Finally, we only focused on preoperative thyroid hormones and we should examine the changes of thyroid hormone levels after CPB.

In conclusion, weight, infection, FT3 level and CPB time are strong predictors of PMV in infants with CHD after CPB. By adjusting these risk factors, the prognosis of infants with CHD may be improved.

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Table 1: Characteristics of enrolled patients with congenital heart disease

Characteristic	All patients (n=165)
Age (days)	36.94±26.60
≤28 days	62 (37.6%)
>28 days and ≤90 days	103 (62.4%)
Gender	
Male	108(65.5%)
Female	57 (34.5%)
Weight (kg)	3.93±0.92
RACHS-1	
Score-1	5 (3.0%)
Score-2	52 (31.5%)
Score-3	64 (38.8%)
Score-4	41 (24.9%)
Score-5	3 (1.8%)
Score-6	0(0%)
Type of Surgery	
ASD	3 (1.8%)
VSD	16 (9.7%)
VSD+ASD	59 (35.8%)
COA/IAA	23(13.9%)
TAPVC	25(15.2%)
TGA	21 (12.7%)
PA-VSD	4(2.4%)
DORV	3(1.8%)
Other	11(6.7%)
Operative factors	
CPB time (min)	114.56±80.38
ACC time (min)	47.94±23.30
MV time (n=150, min)	127.08±126.95
Infection	75(45.5%)
ICU mortality	15 (9.1%)
Pre-operative thyroid function	
FT3 (pmol/L)	5.00±1.51
FT4 (pmol/L)	21.02±5.93
TT3 (nmol/L)	1.90±0.55
TT4 (nmol/L)	120.23±33.95
TSH (μIU/ml)	5.54±5.92

RACHS-1, Risk Adjustment in Congenital Heart Surgery-1; ASD, atrial septal defect; VSD, ventricular septal defect; COA, coarctation of aorta; IAA, interrupter aortic arch; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; PA, pulmonary atresia; DORV, double outlet right ventricular; CPB, cardiopulmonary bypass; ACC, aortic cross-clamping; FT3, free triiodothyronine; FT4, free thyroxin; TT3, total triiodothyronine; TT4, total thyroxin; TSH, thyroid stimulating hormone.

Table 2: Characteristics of patients according to PMV group and non-PMV group

Characteristic	Non-PMV (N=57)	PMV (N=93)	Death (N=15)	P value
Age (days)	44.74±25.27	35.44±26.91	16.60±16.43	**0.001**
≤28 days	10(17.5%)	41(44.1%)	11(73.3%)	**0.000**
Female	27(47.4%)	30(32.3%)	0(0%)	**0.002**
Weight (kg)	4.28±1.01	3.79±0.83	3.47±0.71	**0.001**
RACHS-1≥4	6(10.3%)	29(31.2%)	10(58.8%)	**0.000**
Infection	17(29.8%)	47(50.5%)	11(73.3)	**0.004**
Pre-operative thyroid function				
FT3 (pmol/L)	5.29±1.23	4.99±1.67	4.05±0.99	**0.017**
FT4 (pmol/L)	20.83±5.05	21.36±6.46	19.63±5.73	0.552
TT3 (nmol/L)	1.96±0.49	1.91±0.59	1.58±0.33	**0.050**
TT4 (nmol/L)	116.26±33.82	124.93±34.24	106.24±28.24	0.077
TSH (μIU/ml)	5.66±5.45	5.09±4.93	7.83±11.15	0.246
Operative factors				
CPB time (min)	72.30±44.82	133.74±89.65	156.20±57.08	**0.000**
ACC time (min)	36.98±16.63	52.02±24.80	64.33±18.04	**0.000**

Abbreviations as in Tables 1.

Table 3: Multivariate logistic regression, odds ratio of variables for predicting PMV in patients with congenital heart disease after cardiopulmonary bypass

Variables	B	S.E.	Wald	df	P value	OR	95% C.I. for OR	
							Lower	Upper
Gender	0.724	0.431	2.825	1	0.093	2.062	0.887	4.795
Neonate	0.355	0.522	0.464	1	0.496	1.427	0.513	3.965
Weight	-0.734	0.271	7.326	1	**0.007**	0.480	0.282	0.817
RASCH-1≥4	0.052	0.654	0.006	1	0.936	1.054	0.292	3.799
FT3	-0.799	0.352	5.138	1	**0.023**	0.450	0.225	0.898
TT3	1.689	0.968	3.075	1	0.079	5.464	0.819	36.454
CPB time	0.017	0.007	6.221	1	**0.013**	1.017	1.004	1.030
ACC time	0.000	0.017	0.000	1	0.990	1.000	0.968	1.033
Infection	-1.000	0.437	5.230	1	0.022	0.368	0.156	0.867
Constant	2.615	1.552	2.840	1	0.092	13.674		

Abbreviations as in Tables 1.