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ORIGINAL ARTICLE

Recurrent Extubation Failure Following Neonatal Cardiac Surgery Is Associated with Increased Mortality

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Abstract

Extubation failure (EF) following neonatal cardiac surgery is associated with increased mortality. Neonates who experienced EF twice or more (recurrent EF) may have worse outcomes than those who have a single EF or no-EF. The aims of this study are to investigate the in hospital mortality for neonates with recurrent EF compared to those with single or no-EF, and determine factors associated with recurrent EF. Neonates' ≤ 28 days who underwent cardiac surgery from January 2008 to December 2019 were included. EF was defined as unplanned reintubation within 72 h after a planned extubation. 1187 (18 recurrent EF, 84 single EF and 1085 no-EF) neonates were included. Recurrent EF occurred in 18 (17.6%) of 102 neonates undergoing a second extubation. The median time (IQR) to reintubation after the first and second extubations were similar, being 20.9 (3.3–45.2) versus 19.4 (5.5–47) h. The reason for a second-time EF was respiratory in 39% and cardiovascular in 33%. Recurrent EF and single EF was associated with increased mortality (odds ratio, 95% confidence interval (CI) 23.5, 6.9–79.9) and (odds ratio, 95% CI 5.2, 2.3–12.0) compared to no-EF. Based on the final model with risk adjustment, predicted mortality was 29.0% in recurrent EF, 6.5% in single EF, and 1.2% in no-EF. First-time EF due to cardiovascular compromise was associated with recurrent EF (odds ratio, 95% CI 3.1, 1.0–9.7). This study confirmed that patients with recurrent EF have a high morality. Neonates with a cardiovascular reason for first-time EF are more likely to have a recurrent EF than those with other causes.

Keywords Extubation failure · Recurrent · Morality · Neonate · Cardiac surgery · Risk factor

Background

Previous studies have demonstrated that extubation failure (EF) occurs in 12–18% of neonates after cardiac surgery and is associated with increased mortality (8–30%), prolonged length of stay in the pediatric intensive care unit (PICU) and hospital [1–4]. Several reports have shown that the etiology of EF was diverse including residual cardiac issues, respiratory or tracheal pathology, upper airway obstruction, diaphragmatic palsy, sepsis, or bleeding [4–6]. Some causes are amenable to simple treatments which will increase the likelihood of subsequent successful extubation, whilst other causes are more complex and may involve further surgery or be associated with complex congenital malformations [7].

We hypothesized that neonates experiencing EF twice or more (recurrent EF) may have a higher mortality than neonates experiencing EF once (single EF) or those experiencing no EF (non-EF). It was unclear as to the likely causes of each type of EF and whether this was important to ultimate outcome. Hence this study was done with the primary aim of investigating the hospital mortality among recurrent EF, single EF and non-EF. Secondary aims were to explore the reason of second-time EF, and the association between first EF due to cardiovascular compromise and outcomes.

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Methods

Study Design and Participants

This is a single-center retrospective cohort study. The paediatric intensive care unit at the Royal Children's Hospital Melbourne is a 30-bed combined medical-surgical PICU. All patients after cardiac surgery are admitted to the cardiac pod in the PICU except premature neonates after patent ductus arteriosus ligation. We included all neonates who were 28 days or younger at cardiac operation and admitted to the PICU from January 1, 2008 to December 31, 2019. This study included only the first cardiac surgery for each neonate during the study period. Exclusion criteria included unplanned extubation, no extubation attempt, withdrawal prior to the extubation attempt and tracheostomy.

Definitions and Data Collection

EF was defined as unplanned reintubation within 72 h after planned extubation. The recurrent EF was defined as those who underwent EF twice or more after cardiac surgery. The single EF was defined as those who had EF once. Non-EF was defined as those who had no EF. The following data were retrospectively collected from the medical chart; patient characteristics and preoperative data (sex, gestation, weight, date of birth, date of surgery, date of PICU admission, cardiac diagnosis, comorbidities), operative data (risk adjustment in congenital heart surgery-1 (RACHS-1) category, cardiopulmonary bypass (CPB) time), peri-extubation data (the date and timing of extubation and reintubation, respiratory support post extubation), and outcomes (hospital death, PICU and hospital length of stay). RACHS-1 category was classified as low, medium, high RACHS-1 category based on the mortality in previous literatures. The cause of EF was chosen from a preset table of the etiology of EF by an investigator (S.M.) using information from the medical chart, laboratory result, radiology, echocardiography and other imaging, and conference report. If there are two or more etiologies, the primary one was decided in discussions among study investigators. In cases where there was any uncertainty as to the cause of EF, the cause was ascertained by another investigator (S.P.N.) until two investigators reached an agreement. Among deceased patients without extubation attempt, they were considered to have treatment withdrawal if associated words such as palliation or treatment withdrawn due to fertility were documented in medical records.

Statistical Analysis

Collected data were presented as a number with the percentage for dichotomous variables and median with interquartile range (IQR) for continuous variables. For the analysis for hospital mortality among recurrent EF, single EF and non-EF, a multivariable logistic regression model was developed by adjusting with preset study covariates (age, sex, gestation, chromosomal abnormality, CPB time, preoperative PICU admission, and RACHS-1 category). The predicted risk for hospital mortality by category of EF for the neonate after cardiac surgery was estimated from the final logistic model with covariates adjusted at the mean of observed values. Among 102 neonates who experienced EF once or more, the outcome was compared by the reason of reintubation (cardiovascular or the others) using a logistic regression model after adjusting with same study covariates. Two-tailed p values less than 0.05 were considered significant. STATA 14 (Stata Corp LLC, College Station, TX, USA) was used for all statistical analyses.

Results

During the study period, 1253 neonates underwent cardiac surgery. After excluding 56 neonates who met the exclusion criteria prior to the first extubation, 1197 underwent extubation. 9.4% (112 out of 1197) neonates failed (Fig. 1). Ten of 112 reintubated neonates were excluded from the analysis prior to the second extubation attempt. 17.6% (18 out of 102) experienced recurrent EF. 1187 neonates (18 recurrent EF, 84 single EF, 1085 non-EF) were included for the analysis. The characteristics of included patients are described in the Table 1. The overall hospital mortality was 3.3%. Among the excluded 13 neonates who had an unplanned extubation, 11 were successful (non-EF), 1 failed and extubated successfully the next time and 1 died after 46 days in the PICU.

The crude mortality in recurrent EF, single EF, and non-EF were 33.3% (6 out of 18), 13.1% (11 out of 84), and 2.0% (22 out of 1085) (Fig. 2a). A logistic regression model showed higher hospital mortality in recurrent EF (odds ratio 23.5, 95% confidence interval (CI) 6.9–79.9, $p < 0.001$) and single EF (odds ratio 5.2, 95% CI 2.3–12.0, $p < 0.001$) compared to non-EF after adjusting for study covariates. The predicted risk of hospital mortality by EF categories after adjustment of the study covariates are shown in the Fig. 2b, providing the predicted mortality of 29.0% in recurrent EF, 6.5% in single EF, and 1.2% in non-EF. Recurrent EF was associated with prolonged length of stay in PICU and hospital (Table 2). The Hosmer–Lemeshow goodness of fit test showed p value of 0.30. When recurrent EF was compared to single EF among 102 neonate who experienced EF once or more, neonates with recurrent EF nearly had a fivefold increased odds of death (odds ratio 4.8 (95% CI 1.2–19.2), $p = 0.02$).

The proposed reason for recurrent EF was respiratory (39%), cardiovascular (33%), upper airway obstruction

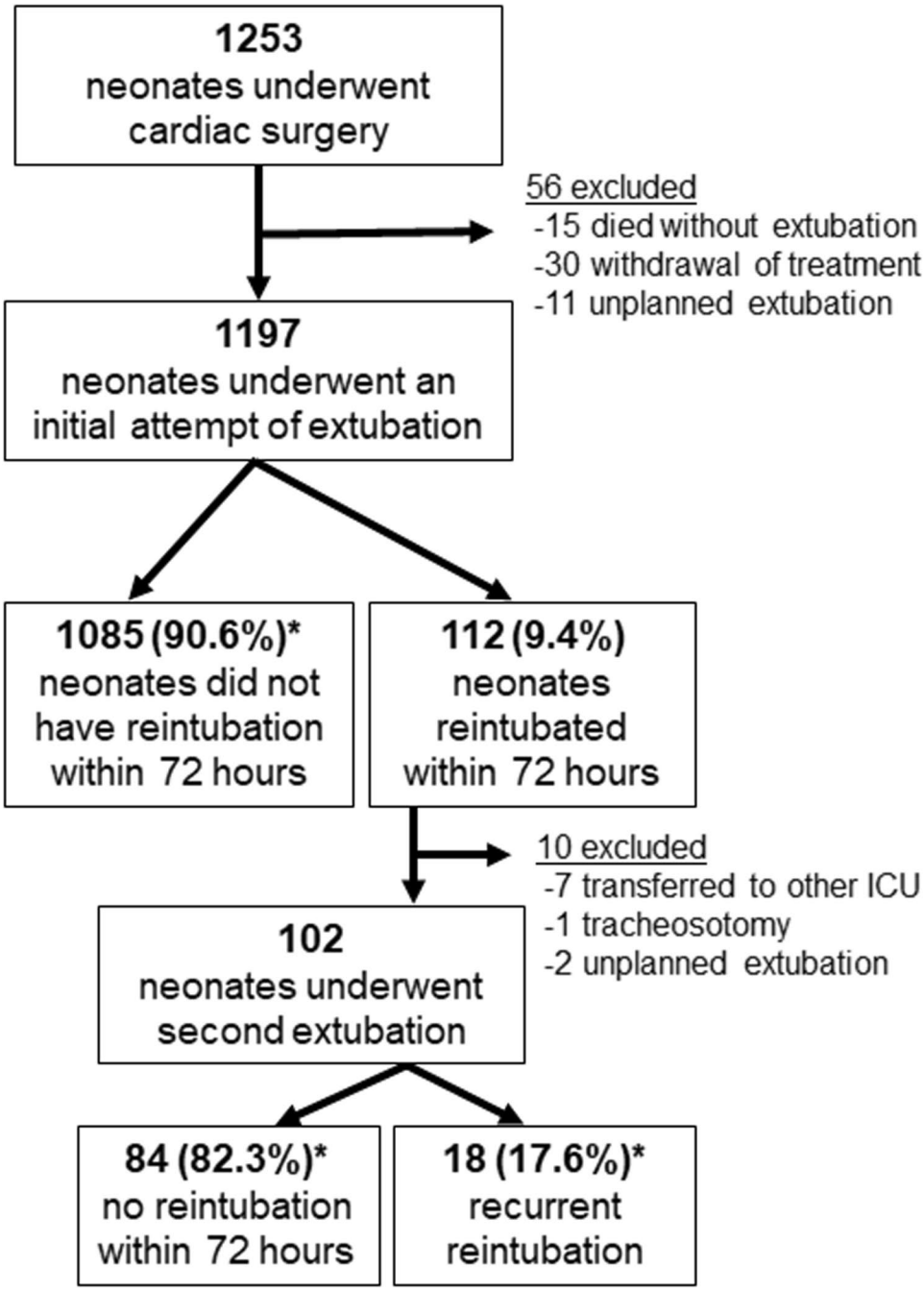

Fig. 1 Study flow. *After excluding 66 neonates who met exclusion criteria, 1187 neonates (18 with recurrent extubation failure, 84 with single extubation failure, and 1085 without extubation failure) were included for analysis. (Among the excluded 13 neonates who had an unplanned extubation, 11 were successful, 1 failed and extubated successfully the next time and 1 died after 46 days in the PICU)

(6%), and others (22%) (Appendix Table 4). Characteristics of first-time and second-time EF is described in the Table 3. The median (IQR) time to reintubation after second extubation attempt was 19.4 (5.5–47) h. Thirteen of eighteen neonates with recurrent EF were placed on continuous positive airway pressure (CPAP) immediately after second extubation while 119 of 1085 children with non-EF were extubated to CPAP. 39% (7 out of 18) of recurrent EF experienced second EF due to the same etiology as at first EF; ventricle dysfunction 2, aortic valve regurgitation 1, sepsis 2, tracheomalacia 1, tracheostenosis 1.

Neonates who failed first extubation due to cardiovascular reasons had a higher odds of recurrent EF (odds ratio 3.1 (95% CI 1.0–9.7), $p = 0.048$) and higher hospital mortality (odds ratio 3.7 (95% CI 1.1–12.4), $p = 0.036$) compared to the other reasons for first EF after adjusting for study covariates.

The duration of mechanical ventilation in 102 neonates following first reintubation was 89 (68–134) h. The duration of mechanical ventilation from reintubation to second extubation attempt was associated with a hospital mortality of 13% in < 24 h, 6% in 24–48 h, 5% in 48–72 h, 7% in 72–96 h,

Table 1 Patient demographics

Variable	All patients $n=1187$	Recurrent EF[a] $n=18$	Single EF[b] $n=84$	Non-EF[c] $n=1085$	p
Age at surgery, day	7 (4–12)	4 (3–8)	5.5 (3–10)	7 (4–12)	0.01
Weight, kg	3.3 (2.9–3.6)	3.1 (2.6–3.7)	3.3 (3.0–3.7)	3.3 (2.9–3.6)	0.50
Male	731 (62%)	12 (67%)	54 (64%)	665 (61%)	0.78
Gestational age, week	39 (38–40)	38 (37–39)	39 (37–40)	39 (38–40)	0.04
Chromosomal abnormality	36 (3%)	1 (6%)	2 (2%)	33 (3%)	0.77
Preoperative ICU admission	659 (56%)	14 (78%)	49 (58%)	596 (55%)	0.13
RACHS-1 category					
1–2	187 (16%)	2 (11%)	8 (10%)	177 (16%)	< 0.001
3–4	833 (70%)	11 (61%)	52 (62%)	770 (71%)	
5–6	167 (14%)	5 (28%)	24 (29%)	138 (13%)	
Use of cardiopulmonary bypass	998 (85%)	15 (83%)	76 (90%)	907 (84%)	0.25
Cardiopulmonary bypass time, min	159 (106–204)	163 (120–229)	158.5 (112.5–220.5)	159 (106–203)	0.53
First extubation, POD	3 (2–5)	7 (3–8)	4 (2–6)	3 (2–5)	< 0.001
Second extubation[d], POD	8.5 (6–13)	10 (8–14)	8 (6–12)	–	0.06

Values are provided as numbers (percentages) for categorical variables and as medians (interquartile ranges) for continuous variables. Categorical variables were analyzed using the chi-squared test and continuous variables were analyzed using the Kruskal–Wallis test to compare study characteristics between study groups

ICU intensive care unit, *RACHS* risk adjustment for congenital heart surgery, *POD* postoperative day

[a,b,c]Recurrent EF is neonates who experienced EF twice or more and single EF is neonates who experienced EF only once while non-EF is neonates experiencing no EF

[d]Data among 102 neonates with single or recurrent EF

and 36% in > 96 h. Mechanical ventilation > 96 h was associated with increased mortality (odds ratio 14.9 (95% CI 1.7–128.6.7), $p=0.01$). 30% (31 out of 102) had surgical interventions before second extubation attempt; open heart surgery ($n=3$), regulation of the Blalock–Taussig shunt flow ($n=4$), patent ductus arteriosus ligation ($n=1$), hemostasis ($n=3$), diaphragm plication ($n=4$), aortopexy ($n=1$), abdominal surgery ($n=3$), chest washout ($n=7$), exploration of heart ($n=2$), and permanent pacemaker insertion ($n=3$). The timing of surgical interventions following EF was on the same calendar day in 16, 1–2 days later in 5; 3–4 days later in 5, ≥ 5 days in 5.

Discussion

The main findings of this study are: (1) recurrent EF occurred in 18% of neonates who had a first EF, (2) hospital mortality incrementally increased as neonates experienced EF, and (3) first EF due to cardiovascular reasons was associated with an increased risk of recurrent EF and mortality.

The association between recurrent EF and increased morality could be multi-factorial including patient-factors and ICU system-factors. Regarding patient-factors, we found that approximately 40% of neonates with recurrent EF failed their second extubation for the same reason, which was mainly structural or functional issues in the heart or airway. Previous studies also reported these are common reasons of EF in neonates after cardiac surgery although only first the EF was reviewed [4]. In relation to ICU system-factors, neonates with congenital cardiac disease receiving multiple-periods of mechanical ventilation have an increased risk of nosocomial infection (sepsis, ventilator-associated pneumonia), lung injury secondary to prolonged positive pressure ventilation, deconditioning and weakness with respiratory muscle [8]. Frutos-Vivar et al. reported that among reintubated patients evolving infections after EF was associated with increased mortality [9]. Consequently, one neonate could be affected by multi-factors, especially considering the fact that mortality is often caused by multiple factors including both patient-factors and ICU system-factors.

Importantly, the cause of first-time EF can be a useful indicator to identify the high-risk cohort in neonates following cardiac surgery. In this study, cardiovascular reason for first EF was associated with recurrent EF and increased mortality. Thus, the ventilation plan tailored to neonates with the cause of EF is essential to avoid further ICU-related complications and recurrent EF, which eventually increase the risk of morality. As an example, neonates experiencing EF with advanced heart failure may subsequently need further therapy including surgical interventions, long-term positive pressure support and nutrition plan for weeks or even months until the heart failure recovers. Some units are increasingly using the inotrope rotation therapy with

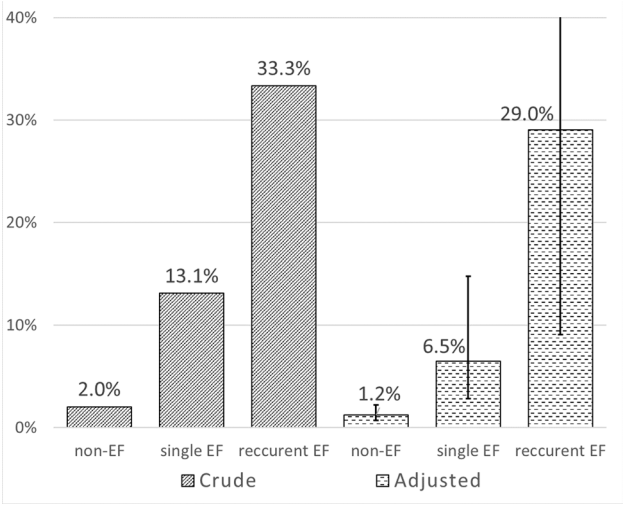

Fig. 2 Mortality by the number of extubation failure (no, once, twice or more) after neonatal cardiac surgery. *EF* extubation failure. This figure shows crude (left) and predicted (right) risk of hospital mortality by the number of EF in neonates after cardiac surgery. 1173 neonates who had complete data were included in a logistic regression model to adjust the risk of hospital mortality for the study covariates (age, sex, gestation, chromosomal abnormality, cardiopulmonary bypass time, preoperative intensive care unit admission, RACHS-1 category). The predicted risk for hospital mortality by category of EF was estimated from the final logistic model with covariates adjusted at the mean of their observed values. Experiencing EF once was associated with mortality that was an absolute 5.3% higher than that if no EF: the probability of death in hospital was 6.5% (95%CI 2.9–14.7%) in single EF versus 1.2% (95% CI 0.7–2.2%) in non-EF ($p < 0.0001$). Experiencing EF twice or more was associated with mortality that was approximately 22.5% higher than if experiencing EF only once: the probability of death in hospital was 29.0% (95% CI 9.1–92.7%) in recurrent EF versus 6.5% (95%CI 2.9–14.7%) in single EF ($p = 0.03$)

long-term positive pressure support for heart failure [10]. The timing of surgical interventions following EF is also important point to consider since the timely interventions are associated with improved outcome compared to later operation if residual lesions are modifiable [11, 12]. By contrast, the timely ventilator weaning and extubation following stabilization of causes of EF may be the priority in neonates experiencing EF due to other causes (e.g., medically modifiable causes), especially considering the fact that prolonged mechanical ventilation after cardiac surgery is associated with a poor outcome and similarly in our study neonates who were ventilated 96 h or more after reintubation had a high mortality [1, 13]. For smoothing ventilation weaning, intensivists should be aware of latent issues deferring ventilator weaning, i.e., some respiratory and cardiovascular compromises could be difficult to recognize during ventilator support but would manifest at the weaning process, including diastolic dysfunction, hyperinflation associated with obstructive airway, reduced lung compliance compensated by baseline respiratory effort, and diaphragmatic dysfunction [8, 14–18]. There are a number of potentially useful tools to assess extubation-readiness during Spontaneous Breathing Trial (SBT) in high-risk patients including monitoring mixed venous oxygen saturation [19], B-type natriuretic peptide [20], respiratory workload [21], echocardiography [22], and ultrasound for diaphragm thickening and/or excursion [23].

Another important point to be studied is the setting of SBT in the second extubation. Thille et al. advocated that the risk of reintubation in high-risk population may become unacceptably high if they were assessed in the same way as unselected low-risk patients [16]. For example, SBT with pressure support may have better ability to pick up patients ready for extubation than SBT with T-piece alone in unselected patients while SBT with pressure support may overestimate the extubation-readiness in high-risk patients, which randomized controlled trials could not have showed due to small cohort size of high-risk patients [16]. Among patients with difficult weaning, Cabello et al. demonstrated greater respiratory and cardiac workload in SBT with T-piece than SBT with pressure support [23]. Compared to commonly-used pressure support of 6–10 cmH2O during SBT at PICU [24, 25], Takeuchi et al. alarmed the possible overestimation of extubation-readiness by SBT with pressure support by demonstrating that SBT with the pressure support of 4 cmH2O could replicate work of breathing post-extubation [21]. We need further evidence with regard to the setting

Table 2 The outcome by the number of extubation failure after neonatal cardiac surgery

	Recurrent EF[a] $n = 18$	Single EF[b] $n = 84$	Non-EF[c] $n = 1085$	p
Hospital mortality, n (%)	6 (33%)	11 (13%)	22 (2%)	< 0.001
ICU stay, day	26 (18–66)	10.5 (7–21.5)	4 (3–7)	< 0.001
Hospital stay, day	67 (33–147)	27.5 (18–44.5)	14 (9–27)	< 0.001

Values are provided as numbers (percentages) for categorical variables and as medians (interquartile ranges) for continuous variables. Categorical variables were analyzed using the χ^2 test and continuous

EF extubation failure, *ICU* intensive care unit

[a,b,c]Recurrent EF is neonates who experienced EF twice or more and single EF is neonates who experienced EF only once while non-EF is neonates experiencing no EF

p value was calculated by using the Kruskal–Wallis test to compare outcomes by category of EF

Table 3 Characteristics of first and second extubation failure after neonatal cardiac surgery

	First-time EF $n=102$	Second-time EF $n=18$
Extubation, postoperative day	4 (2–7)	10 (8–14)
Extubated to		
CPAP	47 (46%)	13 (72%)
HHFNC	18 (18%)	0
Low-flow oxygen or nothing	37 (36%)	5 (28%)
Hours to reintubation	20.9 (3.3–45.2)	19.4 (5.5–47)
Night-time extubation[a]	26 (25%)	3 (17%)
Night-time reintubation[a]	59 (58%)	9 (50%)
Etiology		
Upper airway obstruction	11 (11%)	1 (6%)
Respiratory	44 (43%)	7 (39%)
Cardiovascular	32 (31%)	6 (33%)
Others	15 (15%)	4 (22%)

Values are provided as numbers (percentages) for categorical variables and as medians (interquartile ranges) for continuous variables

EF extubation failure, *CPAP* continuous positive airway pressure, *HHFNC* humidified high-flow nasal cannula

[a]Night-time was defined as from 8 pm to 8 am as per the shift at the study unit

of SBT prior to extubation in re-intubated neonates after cardiac surgery.

There are several challenges for acquiring future evidence, as this cohort is characterized as a special population by following reasons. First, although tracheostomy is a common approach to smooth liberation from respiratory support and avoid complications by reducing sedation requirement and promoting rehabilitation among adults receiving prolonged ventilation, neonates after cardiac surgery may not as good candidates for tracheostomy because of the risk of surgical site infection and long-term airway complications. Second, the efficacy of post-extubation respiratory support could be different from other age groups; bi-level positive airway pressure is rarely feasible in this age as a nature of neonates breathing fast with small tidal volume; positive pressure of non-invasive respiratory support may not be delivered due to open mouth which is common in crying babies. Third, the etiology of EF and comorbidities varies from elder age group post cardiac surgery [26, 27]. Thus, these facts also highlight the importance of future studies in neonates suffering EF.

There are limitations in this study. First, it was a single-center study, limiting the generalizability of our findings to other centers as the mortality in recurrent EF can be influenced by patient-, surgery-, and intensive care-associated factors. Second, the setting of respiratory support pre and post extubation was not reviewed in this study, which could influence the outcome. Third, some potential cause of EF may be missed as some possible causes of EF (delirium, withdrawal, diaphragm muscle weakness, etc.) were difficult to detect in a neonatal study and may have been substituted by other causes like secretion or atelectasis. Forth, mortality is likely to be underestimated by excluding palliated neonates without extubation attempt. The decision of the palliation may vary depending on institutions. Lastly, as this study included twelve years of data, the chronological change in the use of non-invasive respiratory support (CPAP, and humidified high-flow nasal cannula therapy) may have influenced the study result.

Conclusions

Recurrent EF occurred in approximately 18% following first EF in neonatal cardiac surgery and it was associated with an even higher mortality than single EF. This study showed that recurrent EF is an important patient group in terms of high mortality. Neonates with a cardiovascular reason for first time EF are more likely to have a recurrent EF.

Appendix

See Tables 4 and 5.

Table 4 Proposed reasons of extubation failure in second-time extubation attempt after neonatal cardiac surgery ($n = 18$)

Category	%	Reason	*n*
UAO	6	Secretion	1
Respiratory	39	Atelectasis	2
		Pleural effusion	1
		Malacia	1
		Tracheobronchostenosis	1
		Pneumonia	1
		Other	1
Cardiovascular	33	Ventricular dysfunction	2
		Pulmonary hypertension	1
		Aortic valve regurgitation	1
		Sepsis	2
Miscellaneous	22	Surgery	2
		Necrotizing enterocolitis	1
		Imaging	1

From the medical chart, laboratory result, radiology, echocardiography and other imaging, and conference report, the etiology among the category was chosen by a preset table of the etiology of extubation failure. If there are two or more etiologies, the primary one was decided in discussions among study investigators. Where there was doubt regarding ascertainment of the aetiology, a second expert's (S.P.N.) opinion was taken

UAO upper airway obstruction

Table 5 Proposed reasons of extubation failure in first-time extubation attempt after neonatal cardiac surgery ($n = 102$)

Category	%	Reason	*n*
UAO	10	Upper airway edema	6
		Vocal cord paralysis	5
		Unclear	1
Respiratory	42	Atelectasis	7
		Pleural effusion	8
		Pulmonary edema	10
		Diaphragm paralysis	7
		Malacia	3
		Pneumothorax	2
		Tracheo-bronchostenosis	2
		Pneumonia	2
		Muscle weakness	2
		Apnea	2
		Other	4
Cardiovascular	31	Ventricle dysfunction	9
		Pulmonary overcirculation	8
		AV valve regurgitation	5
		arrhythmia	4
		Shunt failure	2
		Aortic valve regurgitation	1
		Other	7
Neuro	2	Over-sedation	2
Miscellaneous	15	Surgery	7
		Sepsis	5
		Bleeding	3
		Imaging	1
		Procedure	1

AV valve atrioventricular valve

[a]Surgery; chest wound wash and debridement in five, pace maker insertion in two, direct left atrial line removal through sternotomy in one

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Author Contributions All authors provided concept/idea/research design. SM provided data collection/data analysis/writing. JT provided and managed patient data. JT, SPN and WB revised and approved the manuscript.

Declarations

Conflict of interest The Authors declare that there is no conflict of interest.

Ethical approval This study was approved by the Royal Children's Hospital Melbourne Human Research Ethics Committee (reference no; 38300), and the need for informed consent was waived.

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