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Delay of extubation in neonates and children after cardiac surgery: impact of ventilator-associated pneumonia

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Abstract *Objective*: This study was undertaken to determine the delay of extubation attributable to ventilator-associated pneumonia (VAP) in comparison to other complications and complexity of surgery after repair of congenital heart lesions in neonates and children.
Methods: Cohort study in a pediatric intensive care unit of a tertiary referral center. All patients who had cardiac operations during a 22-month period and who survived surgery were eligible ($n = 272$, median age 1.3 years). Primary outcome was time to successful extubation. Primary variable of interest was VAP. Surgical procedures were classified according to complexity. Cox proportional hazards models were calculated to adjust for confounding. Potential confounders comprised other known risk factors for delayed extubation.
Results: Median time to extubation was 3 days. VAP occurred in 26 patients (9.6 %). The rate of VAP was not associated with complexity of surgery ($P = 0.22$), or cardiopulmonary bypass ($P = 0.23$). The adjusted analysis revealed as further factors associated with delayed extubation: other respiratory complications ($n = 28$, chylothorax, airway stenosis, diaphragm paresis), prolonged inotropic support ($n = 48$, 17.6 %), and the need for secondary surgery ($n = 51$, 18.8 %; e. g., re-operation, secondary closure of thorax). Older age promoted early extubation. The median delay of extubation attributable to VAP was 3.7 days (hazards ratio HR = 0.29, 95 % CI 0.18–0.49), exceeding the effect size of secondary surgery (HR = 0.48) and other respiratory complications (HR = 0.50).
Conclusion: VAP accounts for a major delay of extubation in pediatric cardiac surgery.

Key words Ventilator-associated pneumonia · Cardiac surgery · Children · Pediatric intensive care · Complications · Extubation

Introduction

Early extubation following cardiac operations in neonates and children is highly desirable. Patients who are extubated soon after surgery spend less time in the intensive care unit (ICU), incur fewer costs, and are safely discharged home earlier [1]. Several review articles, case reports, and case series have demonstrated the wide variety of causes for prolonged times to extubation after cardiothoracic surgery. Among these are stepwise closure of the thoracic cavity [2], low cardiac output, the need for revision of procedure, venous thrombosis [3], immune dysfunction and sepsis [4], multiple system organ failure [5], neurologic sequelae [6] and chylothorax [7], subglottic stenosis [8], laryngeal edema [4], other airway stenosis [9, 10], phrenic nerve paralysis [11, 12] and ventilator-associated pneumonia (VAP) [13]. Finally, the volume of cardiac surgery performed at the center has also been shown to affect in-hospital mortality and length of stay [14].

Many of these complications do not arise alone. Although they often occur in combination with others, previous studies have not attempted to disentangle the delay in extubation attributable to each of these complications. Such estimation of the effect of differing and potentially correlated variables can be achieved by multivariable survival analysis. We hypothesized that VAP would account for a major delay in extubation following cardiac surgery, after adjusting for confounding variables. We aimed to elucidate the resource utilization attributable to VAP in comparison to other complications after pediatric cardiac surgery. Therefore, we reviewed the data of all cases of cardiac surgery from a database which had been prospectively generated by an infectious disease surveillance project.

Methods and materials

Study population

The study was performed at the pediatric ICU (PICU) in a tertiary university hospital. Post-cardiac surgery patients account for approximately 40 % of all care provided by the unit. The center serves the population of Eastern and Southern Switzerland (approximately 3 million people) and recruits some patients from abroad. Patients requiring cardiac surgery between September 1996 and July 1998 were eligible. Patients were included in the present study when they had survived the initial post-operative stabilization period and tolerated transport to the PICU (usually the first or second day after surgery). In this way, we identified all patients who were potentially extubatable.

Database and study type

We performed a retrospective cohort study retrieving information from a prospectively collected research database and clinical information system. This database contains all relevant patient data including parameters collected by specially trained research assistants for the purpose of ongoing cohort studies related to the early diagnosis of nosocomial infection and to the prediction of outcome after cardiac surgery. Where necessary (e. g., chest radiographs) the original material was reviewed.

Primary outcomes

The primary outcome of interest was time to extubation defined as the number of days from intubation to extubation or from the beginning of surgery to extubation in patients who were ventilated before surgery. Extubation on the calendar day of surgery counted as zero days of postoperative ventilation. The primary explanatory variable of interest was VAP after controlling for other complications.

Sedation, pain relief, and weaning procedures

During ventilation patients were sedated with midazolam infusions (0.1–0.3 mg/kg/h) and pain was relieved by morphine infusions (0.01–0.03 mg/kg/h). Some patients required neuromuscular blockade (pancuronium 0.1 mg/kg/dose). Patients were weaned from pressure support using a standard procedure: conditions for extubation were weaning from inotropic support except dopamine or dobutamine not exceeding 5 μg kg min and an inspired fraction of oxygen of less than 0.5. Patients were declared ready for extubation when tolerating a CPAP test, modified from [15], defined as spontaneous breathing on a positive end-expiratory pressure of 4 cm H_2O for 1 h without obvious dyspnoea, diaphoresis or increase in carbon dioxide partial pressure by more than 5 mmHg.

Data collection and definitions

From the research and clinical database we extracted the primary outcome variable *extubation time,* presence or absence of VAP, the time until diagnosis of VAP, and other covariates. Detailed definitions are provided in Table 1.

Statistical analysis

To elucidate the association between covariates and time to extubation, survival analysis was used employing univariate analysis and several multivariable regression models. Patients who died after admission to the PICU while being ventilated were considered censored. Other reasons for censoring were discharge of intubated patients to another hospital.

In a first step we evaluated the unadjusted association between time to successful extubation and complications or risk factors by stratified survival analysis using the Kaplan-Meier method and comparison of the strata by the log rank test. Measures of association (hazard ratios) were derived from Cox regression analysis. We then checked possible associations between the explanatory variables, in particular between VAP, other respiratory complications, complexity of surgery, the need for cardiopulmonary bypass, and the need for secondary operations.

In the next step we controlled the association between time to successful extubation and VAP for potential confounding. All variables or risk factors that showed a significant association in the unadjusted analysis were considered as candidate variables. We developed Cox proportional hazards models using three selection procedures, stepwise selection, backward elimination, and the change in estimate method to derive a model that controlled for confounding and that contained as few variables as necessary. Ties were handled using Efron's approximation for the marginal likelihood.

The resulting model, which had identified five variables, was checked for satisfaction of the proportional hazards assumption by the introduction of a time-dependent covariate [16]. In addition, VAP was modeled as a time-dependent variable. Because a significant interaction between time and VAP was detected, we chose a stratified Cox proportional hazards model. We tested the sensitivity as to differing definitions of time strata. Since the results of these calculations were similar, we chose to present the data adjusted for time strata of 1-week duration (first stratum: 0–7 days). The resulting model no longer violated the proportional hazards assumption, allowing us to calculate the association between time from surgery to successful extubation and VAP, adjusted for other covariates and for time-dependence of VAP.

Table 1 Definition of study variables

Variable	Definition
Primary outcome	
Time until successful extubation	Date of successful extubation or discontinuation from positive airway pressure in tracheostomized patients. Any extubation followed by reintubation within 48 h was regarded as extubation failure. In these cases the transitory extubation period was counted as if the patient had been ventilated.
Co-variables, respiratory system	
VAP	Fever exceeding 38.5 °C, tachypnea, and/or otherwise unexplained increased oxygen requirement, elevated white blood cell count (> 15×10^9 cells/l), a cultured pathogen from tracheal aspirate together with a positive Gram-stain and increased leukocyte contents, plus an infiltration on chest-radiographs persisting for 48 h or more [15].
Time until diagnosis of VAP	Clinical suspicion of pneumonia noted in the patient charts, prescription of antibiotics for suspected infection, and satisfaction of the diagnostic criteria for VAP.
Chylothorax	Pleural effusion requiring drainage, proven by triglycerides and cholesterol levels above plasma levels, a white blood cell count exceeding 1×10^9 cells/l with a lymphocyte fraction exceeding 80 %.
Airway stenosis	Airway stenosis verified by tracheo- or bronchoscopy (more than half of the diameter of a main bronchus or the trachea) or need for reintubation because of inspiratory stridor attributable to subglottic swelling.
Paresis of diaphragm	Diaphragm paresis proven by ultrasound technique or fluoroscopy.
Co-variables, surgical procedures	
Type of surgery	The various types of repair of congenital cardiac defects were ordered into four categories of complexity according to previously published classifications [14]. *Category 1*: e. g., closed valvotomy, repair of atrial septal defect, systemic to pulmonary artery shunt. *Category 2*: e. g., repair of ventricular septal defect, repair of tetralogy of Fallot, revision of procedure. *Category 3*: e. g., valve replacement, repair of total anomalous pulmonary venous connection, repair of truncus arteriosus. *Category 4*: e. g., arterial switch operation, total cavopulmonary anastomosis.
Bypass	Procedures were dichotomized to those that required cardiopulmonary bypass (ECC) and those that did not; bypass time was abstracted from the ECC protocol.
Prior cardiac surgery	Any cardiac surgery prior to current procedure.
Cardiac reoperation	Revision or secondary cardiac surgery within 5 days of primary cardiac surgery.
Secondary closure of thorax	Patient discharged from the operating room with open thorax.
Other secondary surgery related to the procedure	Any other surgical intervention related to primary cardiac surgery performed before the patient was discharged from the unit (including secondary closure of thorax, implantation of pacemaker).
Co-variables, circulatory system	
Prolonged inotropic support	Postsurgical circulatory compromise defined as requirement of > 0.1 µg kg min of epinephrine to maintain mean arterial blood pressure above age appropriate lower limit beyond 3 days post surgery.
Pulmonary hypertension	Patients in whom the mean pulmonary artery pressure exceeded half of the systemic mean artery pressure and who required nitric oxide or prostaglandin infusions for treatment of the condition.
Arrhythmia	Arrhythmia requiring infusion of antiarrhythmic drugs, hypothermia or pacing, but not pacing aimed to increase the heart rate for circulatory improvement in the presence of age appropriate sinus rhythm.
Central venous thrombosis	Thrombosis of a vessel proximal from subclavian or femoral vein leading to edema in the distal region and proven by phlebography.
Co-variables, infections other than lower respiratory tract infections	
Sepsis	Bloodstream infection documented by positive blood cultures, clinical signs of infection, and altered laboratory markers of infection (C-reactive protein > 20 mg/l, leukocytes > 15×10^9/l or < 5×10^9/l).
Wound infection	Inflammation of surgical wound and positive culture with known pathogen.

Costs of PICU care were derived from the financial report of the children's hospital for the fiscal year 1997. The direct PICU costs are calculated from all expenditures for salaries, supplies, and investments. Indirect costs are allocated to revenue centers by a stepdown procedure. The total costs are then divided by the total number of provided hospitalization days. The resulting costs per day of hospitalization represent the average costs per patient with average severity of illness. For purpose of this study we assumed that the weaning procedure from ventilation after cardiac surgery approximates average severity of illness. Values were not discounted. We used the July 1999 exchange rates for conversion of Swiss francs to Euros. All analyses were performed using the SAS system (Version 6.12, SAS, Cary, N.C., USA).

Results

Patient population

During the 22-month study period a total of 292 patients underwent cardiac procedures. Twenty patients (6.2%) died perioperatively and were not considered to be potentially extubatable. The remaining 272 patients (61% males) were eligible. The median age of patients was 1.3 years. Cardiopulmonary bypass was employed in 228 patients (84%). Procedures of complexity category 1 were performed in 75 patients (27.6%), complexity category 2 accounted for 132 cases (48.5%), category 3 comprised 43 patients (15.8%), and in 22 patients (8.1%) procedures of complexity category 4 were performed. Three patients died after enrollment (1.1%), giving rise to a total 28-day mortality of 7.3%, and six patients were transferred to other ICUs before extubation (2.2%). Thus, the total number of censored patients was nine (3.3%). The median time of extubation in the remaining 263 patients was the third postoperative day (95% interval 0.25–25 days). Sixty-six patients (24%) were extubated on the day of surgery. Three surgeons shared 205 procedures (75%) and performed the majority (87%) of surgeries with increased complexity (172 of 197).

VAP and other respiratory complications

We identified 26 cases (9.6 percent of all patients) of pneumonia satisfying our definitions. The cumulative incidence of VAP increased from 4 percent for patients extubated within the first 3 days after surgery to 40 percent in those who remained intubated for longer than 30 days. Ten episodes of VAP (38%) were diagnosed within 3 days after surgery, and a total of 19 episodes were diagnosed before the sixth day after surgery (Fig. 1). Other complications related to the respiratory tract included 11 patients (4.0%) with paresis of the diaphragm, ten patients (3.7%) with chylothorax, and nine patients with airway stenosis (3.3%). A total of 50 patients (18.6%) had one or more respiratory complications. VAP was neither associated with complexity of surgery (Mantel-Haenszel chi-square $P = 0.23$), nor with the use of cardiopulmonary bypass (chi-square $P = 0.22$).

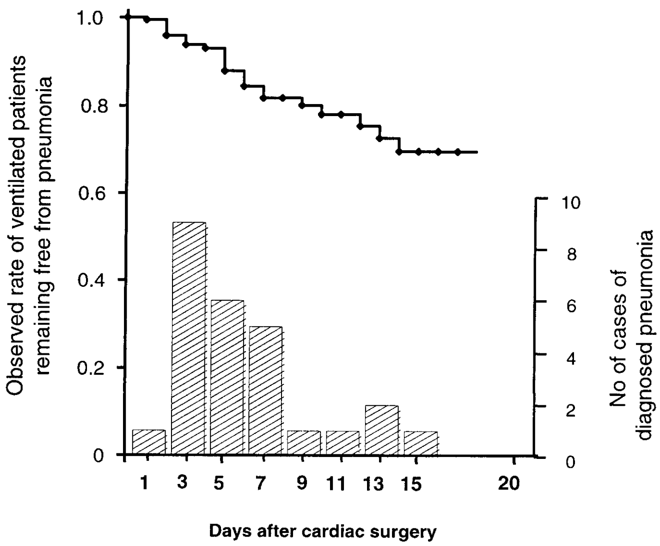

Fig. 1 Time until diagnosis of VAP. The survival curve displays the proportion of ventilated patients in whom pneumonia is not diagnosed in relation to time after surgery. The *vertical bars* (right vertical axis) show the count of patients diagnosed with VAP during every two-day interval after surgery

Association between time to extubation and potential risk factors

Univariate analysis showed a significant association of almost any risk factor or complication with time to extubation (Table 2). The hazard ratio estimates the probability of being extubated on any day in comparison to patients not having the complication or condition. Regarding complexity of surgery, patients are compared with the lowest complexity of surgery. According to the unadjusted analysis, patients with VAP had a 43.4 percent chance of being extubated on any day compared with patients without pneumonia. This effect was of a similar magnitude to the difference between the lowest and highest complexity of surgery. Patients in category 4 had a 40.2 percent chance of being extubated as compared with patients with complexity category 1. To control for trends or variation during the study, we divided the 22-month study period into 2-month intervals. There was neither a significant variation nor a trend of change for time to extubation (chi-square or Mantel-Haenszel chi-square, all $P > 0.05$).

Following univariate analysis we calculated Cox proportional hazard models to examine the relationship of

Table 2 Association with time to final extubation (univariate analysis)

Variable or type of complication	No. (% of total)	Hazard ratio	95% CI	Log rank test *P* value
Age (increment 1 year)		1.094	1.065–1.124	< 0.001
Gender female	106 (39)	1.045	0.814–1.341	0.71
Prior cardiac surgery	63 (23)	0.903	0.677–1.206	0.37
Cardiopulmonary bypass surgery	228 (84)	0.715	0.512–0.998	0.02
Duration of extracorporeal circulation (increment 1 h)	228 (84)	0.685	0.557–0.844	0.004
Respiratory complications				
Pneumonia	26 (10)	0.434	0.286–0.660	< 0.001
Paresis of diaphragm	11 (4.0)	0.415	0.218–0.790	0.003
Chylothorax	10 (3.7)	0.477	0.244–0.932	0.02
Airway stenosis	9 (3.3)	0.313	0.157–0.625	< 0.001
Any respiratory complication	50 (18.6)	0.353	0.255–0.494	< 0.001
Non-pulmonary infections				
Bloodstream infection	14 (5.1)	0.381	0.207–0.701	< 0.001
Wound infection	15 (5.5)	0.417	0.242–0.719	< 0.001
Circulatory complications				
Venous thrombosis	10 (3.7)	0.334	0.163–0.686	< 0.001
Secondary closure of thorax	31 (11)	0.482	0.328–0.709	< 0.001
Revision of procedure	24 (8.8)	0.395	0.249–0.627	< 0.001
Any secondary surgery (e.g., closure of thorax)	51 (19)	0.266	0.188–0.379	< 0.001
Prolonged inotropic support	48 (18)	0.307	0.217–0.435	< 0.001
Pulmonary hypertension	28 (10)	0.356	0.228–0.556	< 0.001
Arrhythmia	27 (10)	0.618	0.411–0.929	0.001
Surgical procedures				
Complexity category 1 (reference group)	75 (27.6)	1.0		
Complexity category 2	132 (48.5)	0.557	0.416–0.747	< 0.002
Complexity category 3	43 (15.8)	0.453	0.305–0.672	< 0.001
Complexity category 4	22 (8.1)	0.402	0.246–0.655	< 0.001

pulmonary complications to time to successful extubation, controlling for complexity of surgery and other potential confounders. Whatever method was used, the same final model resulted that included the following variables: other respiratory complications, prolonged inotropic support, need for secondary surgery, and age. After controlling for these variables, neither complexity of surgery (Wald chi-square, $P = 0.15$) nor pulmonary hypertension ($P = 0.14$) or any other risk factor (all $P > 0.2$) retained a significant association. Finally, we examined whether the association of VAP and time to extubation changed over time on the ventilator by introduction of a time covariate. We reanalyzed our data using several models including time-dependent covariates (time to diagnosis of VAP), interaction terms of time with the diagnosis of VAP, and models stratified for time. The results from the more elaborated models (data not presented) did not differ from the simpler model, which used strata of 1-week duration. The analysis showed that as time after surgery increased, the delay in time to extubation which was attributable to VAP decreased (data not shown).

In order to arrive at an appropriate summary estimate for the effect of VAP, we used a stratified Cox proportional hazards model, which controlled for time-dependence of VAP. The adjusted hazard ratio amounted to 0.293 (95% CI 0.18–0.49). The coefficients and estimates of the effect size for the other covariates are presented in Table 3. This adjusted analysis showed the smallest hazard ratio for VAP as compared to other factors such as secondary surgery, prolonged requirement of inotropic support, and other respiratory complications. The smaller a hazard ratio, the lower is the probability of a patient of being extubated at any given time when compared to patients without the condition.

Figure 2 displays the estimated time to extubation for patients with and patients without VAP based on this adjusted analysis. The curves are calculated assuming the most frequent category of surgery (category 2), the median age of the study population (1.3 years), and no other complications. The adjusted median time to extubation was 1.5 days for patients without VAP and 5.2 days for patients with VAP ($P < 0.001$). Assuming that a 3.7 day delay in extubation corresponded to the same delay in discharge from the PICU, the median costs associated with each case of VAP would amount to € 7500.

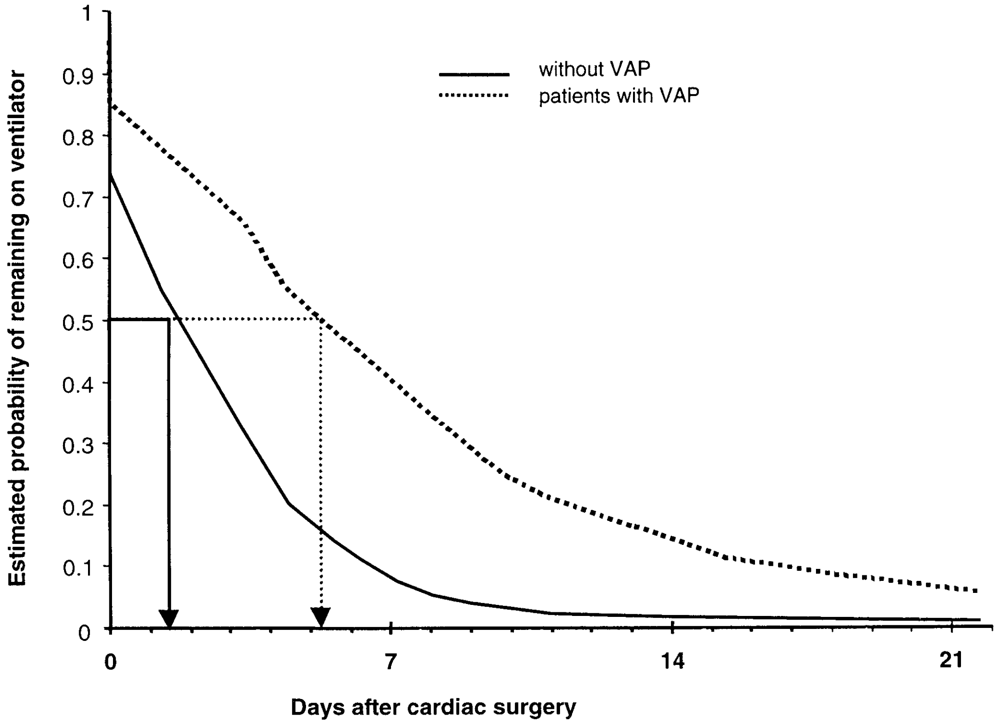

Fig. 2 Predicted time to extubation for patients with (VAP), adjusted analysis. The *dotted line* represents the predicted time for patients with VAP, the *full line* depicts the time to successful extubation for patients without VAP. For all other criteria the data from the study population are adjusted for confounding by complexity of surgery, age, and other complications

Discussion

We aimed to elucidate the delay in extubation attributable to VAP in comparison to other known risk factors for delayed extubation after cardiac surgery in neonates or children. Because univariate analysis showed a significant association between time to extubation and most known risk factors, we performed multivariable analysis. The multivariable analysis identified VAP, other respiratory complications (chylothorax, diaphragm paresis, airway stenosis), requirement for prolonged inotropic support, a requirement for secondary surgery, and a younger age as significant predictors of time to extubation.

The cumulative risk of VAP increased over time. VAP occurred in one out of ten patients. The overall rate of VAP was similar to all other respiratory complications (10.4 percent of all patients, comprising diaphragm paralysis, chylothorax, and airway stenosis), other infections (11.6%), secondary closure of thorax (11%), pulmonary hypertension (10.4%), and arrhythmias (10%). The adjusted analysis estimated the median attributable delay to extubation for a patient with surgery of moderate complexity to 3.7 days.

Like VAP, other respiratory complications, secondary surgical procedures (e.g., delayed closure of thorax), and prolonged inotropic support conferred a risk of delayed extubation. The hazard ratios obtained from the adjusted model (Table 3) reveal that the effect size for VAP showed a trend towards exceeding that of the other three factors. The final model attributed a positive effect to age: older children were extubated earlier than newborns or infants. In contrast to previous studies that employed less adjustment [17, 18], neither complexity of surgery nor cardiopulmonary bypass time remained significant predictors of extubation after the mentioned variables were included in the model. All other conditions, which showed a significant association

Table 3 Parameter estimates in the stratified model adjusting for confounding

Parameter	Estimate	Standard error	Wald chi-square *P*	Hazard ratio (95% CI)
VAP	–1.229	0.259	< 0.0001	0.293 (0.176–0.486)
Other respiratory complications[a]	–0.728	0.274	0.0078	0.483 (0.282–0.825)
Prolonged inotropic support	–0.940	0.221	< 0.0001	0.391 (0.253–0.602)
Secondary surgery[b]	–0.684	0.198	0.0006	0.505 (0.342–0.744)
Age (years)	0.111	0.016	< 0.0001	1.118 (1.084–1.153)

[a]Any of: chylothorax, diaphragm paresis, airway stenosis
[b]Any secondary surgery related to the primary operation, e.g., revision, secondary closure of thorax

in the univariate analysis and which have been reported as risk factors for delayed extubation, failed to retain this association in the adjusted analysis. Our findings underscore that the increased rate of complications associated with higher complexity of surgery – but probably not surgery per se – accounts for the major proportion of prolonged time on the ventilator observed in patients with more complex procedures.

The potential savings by reducing the rate of VAP [19] are of similar magnitude to the effects from other measures aimed at reducing time on the ventilator. Early extubation after cardiac operations has been shown to be practicable even in newborns and infants subjected to complex operations after changing anesthetic, surgical, and perfusion management procedures. Patients with early extubation had 3.4 days shorter hospitalization in the ICU and 7.6 shorter postoperative hospitalization stays [1].

The strength of this study is the adjusted analysis allowing the identification of the main predictors of delayed extubation from a large set of risk factors and complications. However, several limitations must be acknowledged. The results are not generalizable to centers that have large caseloads (more than 300 procedures per year) or to those with very small caseloads. Nevertheless, a majority of centers performing pediatric cardiac surgery have caseloads similar to the study center (approximately 150 per year) [14]. The retrospective nature of the design introduces potential misclassification bias for all data that needed to be abstracted retrospectively. VAP comprises a spectrum ranging from limited focal processes to confluent bronchopneumonia. A more liberal definition than our criteria would have reduced the observed effect size in comparison to the unknown true effect size. Moreover, although our attempts to control for other covariates exceed that of other reports, sophisticated statistical analysis is no proof of causation. Some, but certainly not all, cases of infections associated with surgery may be preventable. An example is the treatment of nasal carriers of *Staphylococcus aureus* to prevent dislocation of bacteria into the respiratory tract during intubation [20]. Whether interventions targeted to reduce the rate of VAP or other complications translate into improved outcomes and relevant costs savings remains to be elucidated by prospective trials. Our data provide a starting point for the design and the power estimation of such trials.

We conclude from multivariable survival analysis that VAP after pediatric cardiac surgery is associated with a median delay in extubation of 3.7 days. The associated costs amount to € 7500 per case.

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