SUPPLEMENTARY DIGITAL CONTENT

Extubation Failure in Brain Injured Patients: Risk Factors and Development of a Prediction Score in a Preliminary Prospective Cohort Study.

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Methods

Patients and setting

The study was performed in a 13 beds NeuroICU and 2 general ICUs (17 and 15 beds respectively) of a university hospital.

Patients were deemed eligible if: intra-cranial pressure < 20 mmHg and cerebral perfusion pressure > 60 mmHg, pressure support ≤ 8 cmH_20 in pressure support ventilation (PSV), positive end expiratory pressure (PEEP) ≤ 5 cmH_2O, pulsed oxymetry (SpO_2) ≥ 92% with inspired fraction of oxygen ≤ 40%, respiratory rate (RR) ≤ 35 min^{-1}, $PaCO_2$ ≤ 45mmHg, expired tidal volume > 7 $mL.kg^{-1}$ of ideal body weight, temperature < 38,5°C, hemodynamic stability with norepinephrine < 0.2 $\mu g.kg^{-1}.min^{-1}$ and mean arterial pressure > 65 mmHg. Management of our patients follows international guidelines requesting negative fluid balance once the acute stage of the disease has resolved.[1]

After resolution of acute organ dysfunctions notably elevated intracranial pressure (ICP) and sedative drugs withdrawal, eligibility for a spontaneous breathing trial (SBT) was daily assessed. SBT consisted of one hour in PSV with pressure support 6 to 8 cmH_2O and no PEEP. SBT was conducted during the morning. In case of failure, prior respiratory parameters were set back and eligibility for SBT was reassessed daily.

SBT was considered successful if at the end of the trial RR < 35 min^{-1}, SpO_2 > 90%, no evidence of clinical respiratory failure, heart rate < 120 min^{-1} or variation < 20%, systolic blood pressure < 200 mmHg or > 90 mmHg, no neurologic deterioration or agitation. SBT was stopped if one of these events occurred.

Time between the end of a successful SBT and extubation did not last more than one hour.

No systematic cuff leak test was realized.

Respiratory failure necessitating reventilation was defined as the occurrence of at least 2 signs among: oxygen therapy > 9L.min^{-1} to maintain SpO_2 > 90%, RR > 35 min^{-1} with accessory respiratory muscles involvement, respiratory or cardiac arrest, major tracheal secretions with inadequate cough, $PaCO_2$ > 50 mmHg with pH < 7,35, heart rate > 120 min^{-1}, systolic blood pressure > 200 mmHg or < 90 mmHg.

The choice between non-invasive ventilation or endotracheal intubation was let to the judgment of the physician in charge of the patient. Non-invasive ventilation consisted of 2 levels pressurization via a face-mask. Only standard oxygen therapy was used in the study without high flow devices.

Data Collection

Patients were prospectively screened before the first SBT and clinically assessed immediately after the end of the successful SBT and prior to extubation, during ICU stay and at 6 months. Only the first extubation for each patient was evaluated. Evaluation and follow up were exclusively done by 4 senior intensivists working in the 3 ICUs (RC, TG, SK and JM). Data collected prior to extubation consisted of:

- at admission : demographic parameters, Simplified Acute Physiologic Score (SAPS) II, type of neurologic lesion (TBI, SAH, supra or infra-tentorial ICH, supra or infra-tentorial AIS, HIE), GCS prior to intubation, pupillary abnormality and reactivity, brain stem reflexes, tobacco and alcohol use, comorbidities (respiratory (chronic respiratory failure, COPD), cardiac (chronic heart failure, coronaropathy), neurologic (prior

stroke), diabetes mellitus), characteristic of intubation (pre-hospital, difficulty defined as more than 2 laryngoscopy or use of an alternative intubation strategy)[2]

- at the end of a successful SBT and prior to extubation : number of failed SBT, duration of mechanical ventilation, GCS with 1 point for verbal (total score on 10 points due to inability to assess verbal component of the score with intubation),[3] Richmond Agitation Sedation Score (RASS),[4] Behavioral Pain Scale (BPS),[5] Full Outline of UnResponsiveness (FOUR) score with 3 components (Eyes, Motor, Brainstem Reflexes)[6] (Respiration item systematically rated 1 with intubation and breathes above ventilator rate for every patients in our cohort since they sustain pressure support ventilation), Coma Recovery Scale Revised (CRS-R) with its 6 components (auditory, visual, motor, oromotor/verbal, communication, arousal)[7] with specificity related to inability to vocalize due to the endotracheal tube (item 2 of the oromotor/verbal function scale (« vocalization/oral movement ») validated if oral movement compatible with vocalization attempt is observed and item 3 (« intelligible verbalization ») validated if one could recognize words on patient lips or if the patient is able to write words), CAM ICU,[8] blood gas parameters the morning before last SBT (PaO_2/FiO_2 ratio, $PaCO_2$, pH), rapid shallow breathing index (f/Vt),[9] heart rate, blood pressure, RR, SpO_2, weight change from admission, intercurrent neurologic (intracranial hypertension, hydrocephaly, seizure, craniectomy, symptomatic vasospasm, thrombophlebitis), respiratory (pneumonia, ARDS, pleural effusion, pneumothorax, pulmonary embolism) and hemodynamic (acute cardiac failure, ischemic cardiomyopathy) events. Cough was considered preserved if present either spontaneously and/or during suctioning irrespective of any quality or strength assessment. Deglutition was considered effective if clinical observation of spontaneous cephalic thyroid cartilage displacement was present. Gag reflex was tested by external bilateral stimulation of the back of patient's tongue, soft palate and posterior pharyngeal wall (trigger zones) with a wooden tip.[10] Gag reflex was considered present with observation of laryngeal spasm and vomiting effort. (see

references for details about the scores used)

Data collected after extubation and during ICU stay consisted of etiology of extubation failure if occurred: cardiac, stridor, hypersecretion, pneumonia, aspiration, atelectasis and neurologic (defined as intracranial structural complication: cerebral rebleeding, acute stroke, encephalitis…), delay of extubation failure if occurred with dichotomization before and beyond 48 hours, days on mechanical ventilation (invasive and non-invasive), number of endo-tracheal intubation, tracheostomy, ICU length of stay, death in ICU, Glasgow Outcome Scale (GOS) (with 6 levels corresponding to 1=death ; 2=vegetative state ; 3=severe disability :minimally conscious state ; 4=severe disability other than minimally conscious state : able to execute simple orders, inability to live independently ; 5=moderate disability : able to live independently, inability to work or study ; 6=good recovery : able to work or study)[11] at ICU discharge. Hospital length of stay and GOS at 6 months after the neurologic insult were also recorded by means of a phone call to the patient or a next of kin.

General management: all patients had orotracheal intubation, cardio-respiratory monitoring, a central venous catheter, an arterial line with arterial blood gas analyses at least every morning and on demand, a nasogastric tube for enteral nutrition unless contraindicated. Fluid management was aimed at maintenance of a negative fluid balance after stabilization.

Duration of mechanical ventilation was defined as the time between intubation (which systematically means beginning of invasive mechanical ventilation in our study) and definitive liberation from invasive mechanical ventilation (either provided by an orotracheal tube or tracheostomy) and non invasive mechanical ventilation. Timetables of events were monitored and one day was defined as a complete 24 hours consecutive period.

Weaning of non invasive mechanical ventilation was considered acquired after 48 hours. Spontaneous breathing beyond 48 hours through a tracheostomy was considered the end of ventilator support. In case of extubation failure, each mechanical ventilation (invasive and non invasive) periods were summed.[12]

Statistical Analysis

It seemed difficult to propose a sample size estimation according to literature in order to develop and validate a simplified pragmatic score predictive of extubation failure in this category of patients. Numerous rules-of-thumb have been suggested for determining the minimum number of subjects required to conduct multiple regression analyses but they are heterogeneous and often with minimal empirical evidence. For multiple regression models, some authors suggested variable ratios of 15:1 or 30:1 when generalization was critical [13-16]. Considering these works and expected extubation failure rate between 20% and 30%, we proposed to include at least 120 subjects to highlight 3 to 5 predictive factors. A post-hoc statistical power estimation was proposed.

All analyses were performed using Stata software (version 13, StataCorp, College Station, TX) and done for a two-sided type I error of α=5%. Patients' characteristics were described by numbers and percentages for categorical parameters. For quantitative values, mean and standard deviations or median with interquartile range were calculated and presented according to statistical distribution (normal distribution of quantitative values was checked by Shapiro-Wilk test). Categorical data were compared using Chi^2 test. Quantitative data were compared between independent groups (extubation success/failure) using Student *t*-test or Mann-Whitney test when assumptions of *t*-test were not met (normality studied using Shapiro-Wilk test and homoscedasticity using Fisher-Snedecor test). A multivariate analysis was performed using logistic regression models by stepwise approach according to univariate results ($P<0.10$)[17,18] and clinical relevance.[19,20] Results were expressed with odds-ratios (OR) and 95% confidence interval (CI). The final model was validated by a two-step bootstrapping process. In each step, 1,000 bootstrap samples with replacements were created from the training set. In the first one, using the stepwise procedure, we determined the percentage of models including each of the initial variables. In the second step, we independently estimated the logistic regression parameters of the final model. The bootstrap estimates of each covariate coefficient and standard errors were averaged from those

replicates. Log-likelihood measured the goodness-of-fit of a model. Following these multivariate analyses, a ROC curve was plotted for the final model, and area under the curve (AUC) was estimated.[21] A score predicting the extubation failure was estimated according to OR values. The threshold value of this score was determined according to usual recommendations by estimating several indexes as Youden, Liu and efficiency. Sensitivity, specificity and negative/positive predictive values were presented with 95% confidence intervals. A sensitivity analysis was performed to study patterns of patients with missing data, considered after analyses as not missing at random (NMAR). These aspects had no impact on results. An analysis of extubation failure before 48 hours was also conducted.

Missing data were investigated. Among failure group, 361 of 4730 (7.6%) and success group, 915 of 10670 (8.6%) data were missing (*P*=0.45). Total percentage of missing data was 8.3%. No data was missing for primary outcome.

Results

Sub group of extubation failure before 48 hours

Results of subgroup analyses of extubation failure before 48 hours are presented in Table E1 and E2.

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Tables, Figures and Legends

Table E1. Results of univariate analysis in the subgroup of patients who failed extubation before 48 hours. Criteria associated with extubation failure before 48 hours. Missing patients are the 12 requiring intubation *after* 48 hours. This subgroup analysis allows the comparison between successfully extubated patients and early failure (< 48h). No difference rose from this subgroup analysis compared to delayed extubation failure. Data are presented as means ± SD unless otherwise noted. Scores items are presented as means ± SD to be more illustrative of differences. *Definition of abbreviations:* BPS = behavioral pain scale; CAM-ICU = confusion assessment method for the intensive care unit; CRS-R = coma recovery scale-revised; FOUR = full outline of unresponsiveness; GCS = Glasgow coma scale; HR = heart

rate; RASS = Richmond agitation and sedation scale; RR = respiratory rate; RSBI = rapid shallow breathing index.

Table E2. Results of multivariate analysis in the subgroup of patients who failed extubation before 48 hours. Criteria independently associated with extubation failure before 48 hours. Two models are presented. *Definition of abbreviations:* AUC = area under the curve.

Table E3. Characteristics of patients on successful SBT day. Data are presented as means ± SD unless otherwise noted. *Definition of abbreviations:* ARDS = acute respiratory distress syndrome; MV = mechanical ventilation; SBT = spontaneous breathing trial. Percentages may not exactly total 100% because of rounding.

Table E4. Causes of extubation failure. Neurologic stands for acute intracranial structural complications: cerebral rebleeding, acute stroke or encephalitis. Data are presented as number (percentage). Percentages may not exactly total 100% because of rounding.

Figure E1. Distribution of GCS (total (eye + motor), eye and motor subscales) and percentages of extubation failure. Full ranges of total GCS and subscales are present in our cohort. *List of abbreviations:* N_T = total number of patients presenting with specified score; N_F = number of patients presenting with extubation failure with specified score.

Figure E2. Association of CRS-R item “visual” sub-scores according to statistical distribution and clinical relevance.

Table E1

	Extubation Success (n=97)	Extubation Failure (n=31)	*P*
Neurological examination prior to extubation			
GCS, median [IQR]	9 [8-10]	9 [6.5-10]	0.06
Item "eye", median [IQR]	4 [4-4]	4 [3-4]	**0.019***
Item "motor", median [IQR]	6 [5-6]	5 [4-6]	0.15
RASS, median [IQR]	0 [-1-0]	-1 [-1-0]	0.17
BPS, median [IQR]	3 [3-3]	3 [3-3]	0.60
FOUR score, median [IQR]	12 [11-13]	11 [9-12]	**0.001***
FOUR item "eye"	3.6 ± 0.8	2.9 ± 1.1	**<0.0001***
FOUR item "motor"	3.2 ± 1.1	2.8 ± 1.3	0.16
FOUR item "brainstem"	4.0 ± 0.1	3.7 ± 0.7	**0.001***
CRS-R, median [IQR]	15 [10-19]	11 [8-14]	**0.006***
CRS-R item "auditory"	2.6 ± 1.4	2.3 ± 1.4	0.18
CRS-R item "visual"	3.1 ± 1.4	2.2 ± 1.2	**< 0.0001***
CRS-R item "motor"	3.7 ± 1.6	3.3 ± 1.4	0.28
CRS-R item "oromotor/verbal"	1.3 ± 0.7	1.0 ± 0.7	**0.009***
CRS-R item "communication"	0.9 ± 0.9	0.8 ± 0.8	0.79
CRS-R item "arousal"	2.5 ± 0.7	1.7 ± 0.9	**< 0.0001***
Confusion (CAM-ICU), n (%)	54 (56)	26 (84)	**0.004***
Respiratory examination prior to extubation			
RR, min^{-1}	19,1 ± 5,5	19,1 ± 4.4	0.90
RSBI, f/Vt, $min^{-1}.L^{-1}$	39 ± 19	34 ± 13	0.47
Airways management			
Cough, n (%)	75 (77)	23 (53)	**<0.0001***
Gag reflex, n (%)	83 (86)	19 (61)	**< 0.0001***
Deglutition, n (%)	76 (78)	11 (35)	**< 0.0001***
Miscellaneous			
Weight variation, kg	-0.4 ± 7.9	0.1 ±5.6	0.76
HR, min^{-1}	88.4 ± 16.3	85.5 ± 13.0	0.45

Table E2

	OR (95% CI)	*P*
CRS-R item "visual"	2.3 (1.2-4.4)	**0.01***
Gag reflex	4.1 (1.2-13.7)	**0.023***
Deglutition	3.1 (1.2-8.3)	**0.022***
Cough	3.6 (1.4-9.3)	**0.009***
AUC	0.806 (95% CI 0.72 – 0.90)	

Table E3

	Extubation Success (n = 97)	Extubation Failure (n = 43)	*P*
Failed SBT	1.7 ± 1.4	1.4 ± 0.8	0.24
Days on MV, median [IQR]	17 [10-25]	16 [11-22]	0.88
Arterial gases			
PaO_2/FiO_2, mmHg	335 ± 82	334 ± 94	0.73
$PaCO_2$, mmHg	38.9 ± 5.6	38.8 ± 6.5	0.69
pH	7.45 ± 0.04	7.45 ± 0.04	0.76
HCO_3^-	27.2 ± 3.4	26.7 ± 4.7	0.53
Intercurrent neurologic event, n (%)	61 (63)	26 (61)	0.87
Intercurrent respiratory event, n (%)	76 (78)	35 (81)	0.57
Pneumonia, n (%)	72 (74)	35 (81)	0.28
ARDS, n (%)	17 (18)	6 (14)	0.62
Intercurrent hemodynamic event, n (%)	19 (20)	6 (14)	0.44

Table E4

	Extubation failure (n=43)
Cardiac	1 (2)
Stridor	6 (14)
Hypersecretion	29 (67)
Pneumonia	2 (5)
Aspiration	2 (5)
Atelectasis	3 (7)
Neurologic	0

Figure E1.

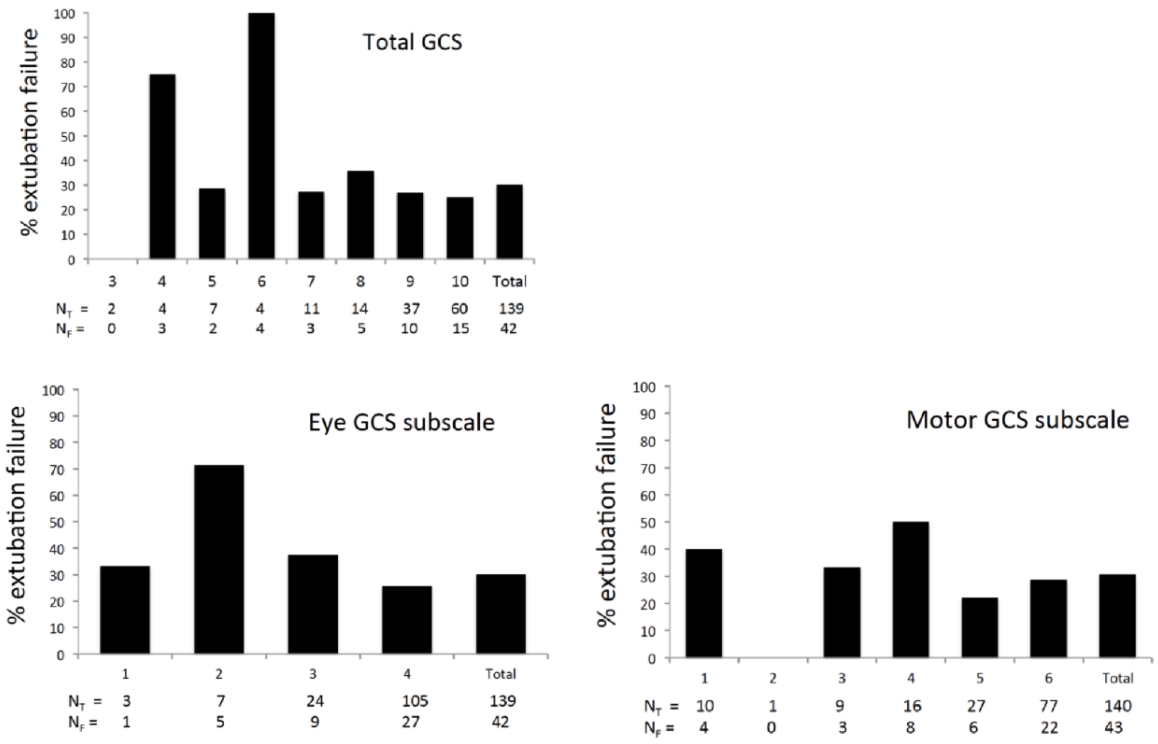
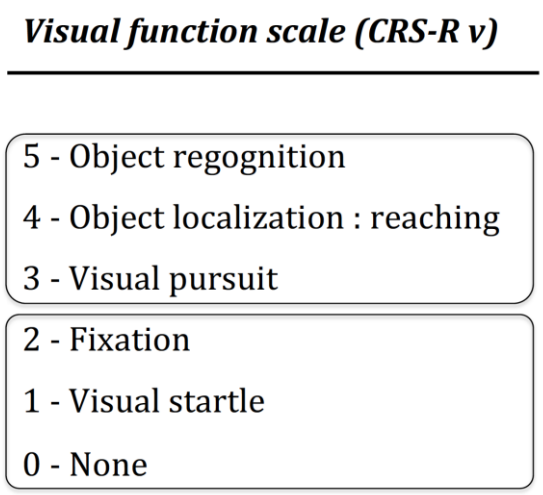

Total GCS
% extubation failure
100
90
80
70
60
50
40
30
20
10
0
3 4 5 6 7 8 9 10 Total
N_T = 2 4 7 4 11 14 37 60 139
N_F = 0 3 2 4 3 5 10 15 42
Eye GCS subscale
% extubation failure
1 2 3 4 Total
N_T = 3 7 24 105 139
N_F = 1 5 9 27 42
Motor GCS subscale
% extubation failure
1 2 3 4 5 6 Total
N_T = 10 1 9 16 27 77 140
N_F = 4 0 3 8 6 22 43

Figure E2


Visual function scale (CRS-R v)
5 - Object regognition
4 - Object localization : reaching
3 - Visual pursuit
2 - Fixation
1 - Visual startle
0 - None