The factors predicting early extubation after targeted temperature management for out of hospital cardiac arrest patients

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Abstract

Out of hospital cardiac arrest patients treated with targeted temperature management may have substantial difficulty in extubation due to multiple organ failure. However, predictive factors of extubation after targeted temperature management remain unclear. We hypothesized that time required for extubation after targeted temperature management is determined by prehospital care and predicted by examinations in emergency department. The purpose of this study was to examine what factors predict early extubation after targeted temperature management.

We performed a retrospective cohort study of out of hospital cardiac arrest patients brought to the emergency room at St. Luke's International Hospital in Tokyo, Japan, between January 2006 and July 2015. We included patients who collapsed out-of-hospital due to a cardiogenic cause, and completed targeted temperature management after return of spontaneous circulation. Primary outcome is the number of days to extubation from admission to the intensive care unit. Using the electronic medical record, we collected data about patient characteristics, prehospital care, and examination in emergency department. Setting tracheostomy cases and in-hospital death cases with intubation as competing risks, the causal relationship between resuscitation condition and primary outcome were assessed with Fine and Gray model analysis.

Of 209 out of hospital cardiac arrest patients who received targeted temperature management during this period, 114 patients completed targeted temperature management with the targeted temperature of 34.0±0.5 °C. After one patient was excluded, there remained 113 eligible patients: 76 patients were extubated, 31 received tracheostomy, and five died in-hospital while being intubated without a tracheostomy. The results of the Fine and Gray model multivariate analysis found that these variables had significant differences: younger age (95% CI of hazard ratio, 0.94 - 0.97); existence of bystander CPR (95% CI of hazard ratio, 1.13 - 3.23); short time to ROSC (95% CI of hazard ratio, 0.94 - 0.99); existence of motor response in ED (95% CI of hazard ratio, 1.37 - 3.94). Prehospital care and examinations on admission can predict early extubation after targeted temperature management. Therefore, this result can be helpful in clinical decision making around targeted temperature management.

Keywords: targeted temperature management, extubation

The factors associated with extubation after targeted temperature management for cardiac arrest patients

Literature Review

Survivors of out-of-hospital cardiac arrest (OHCA) have a very high risk of death and poor neurologic function as Goto (2013) reported. However, both Bernard, et al. (2002) and the Hypothermia after Cardiac Arrest Study Group (2002) reported that targeted temperature management (TTM) improves survival and neurological outcome of OHCA patients. The International American Heart Association guideline (2015) recommends that all comatose adult patients with return of spontaneous circulation (ROSC) after cardiac arrest should have TTM, with a target temperature between 32°C and 36°C selected and achieved, and then maintained constantly for at least 24 hours.

TTM necessarily needs intubation and mechanical ventilation because of the introduction of muscle relaxants. Patients who receive TTM are likely to have range of organ failures. Therefore, such patient’s characteristics make extubation or weaning difficult. Esteban et al. (2002) revealed that the duration of ventilator dependence may cause serious complications such as pneumonia or barotrauma, and it can be associated with high mortality, therefore early extubation is desired. Moreover, Thille, Harrois, Schortgen, Brun-Buisson, & Brochard, (2011) reported that patients who failed extubation had an extremely high mortality rate. Therefore, in daily bedside practice, physicians sometimes have difficulty in judging whether to extubate or not, because patients show a wide variety of disorder of consciousness, heart failure, and respiratory distress which are caused by original diseases or through the TTM maneuver.

Though Sandroni and Geocadin (2015) found that a good prognosis for neurological outcomes is based on examinations 72 hours after TTM, however little is known in terms of extubation after TTM setting. There is little to report about the length of ventilation time after TTM or what factors can predict early extubation for such patients, and to our knowledge, it is only reported as a descriptive report by May T (2015).

We hypothesized that the difficulty of extubation after TTM can be determined by the initial resuscitation condition, and that we can predict the difficulty of extubation after TTM when patients are in the emergency department (ED). The purpose of this study is to recognize what factors contribute to early extubation after TTM, focusing on the prehospital care and clinical examination in the emergency department. If we can predict the timing of extubation after TTM based on patient information upon hospital arrival, we can make safer judgements for extubation in the early hospital phase, and we can manage more strategically, for extubation during TTM, in terms of fluid infusion, usage of sedation, and ventilator weaning.

Method

Study design

We performed a retrospective cohort study of OHCA patients brought to the ED at St. Luke's International Hospital (SLIH) in Tokyo, Japan, who underwent TTM between January 2006 and July 2015. We set inclusion criteria as follows: (1) Participants were patients who collapsed out of hospital, (2) received TTM at SLIH, and (3) survived. Exclusion criteria were as followed: (1) patients who used extracorporeal life support; (2) those who couldn't endure TTM; (3) those who were brought from another hospital; (4) patients who collapsed due to other than cardiogenic etiology, and (5) those who received coronary artery bypass grafting (CABG) before extubation or tracheostomy.

All included patients had to be treated with the same TTM protocol: maintaining 34.0±0.5 °C for 24 hours, and after that rewarmed at the rate of 0.5 to 1.0 °C /12 hours according to our local protocol. During this period, 209 OHCA patients were hospitalized in our hospital and TTM was attempted based on judgements of emergency physicians. Of those 209 patients, 113 were assessed for this study; 96 patients were excluded for the following reasons: 44 - use of extracorporeal life support; 20 - non-cardiac etiology; 27 - use of different protocol in TTM; 4 - cessation of TTM as a result of hemodynamic instability or other critical complication after initiating TTM and 1 - receiving CABG before extubation, tracheostomy, or death. Eventually, 113 patients were eligible as study participants (See Figure). We followed all participant patients until hospital discharge.

Data collection and assessment of outcome

At first, we received ethical approval from the Research Ethics Committee of St. Luke's International Hospital, Tokyo, Japan (approval code: 17R-129). The institutional board waived the need for informed consent, because data were collected retrospectively in an anonymous fashion, and without intervention.

All cardiac arrest data were collected from Utstein style in order to maintain reporting uniformity. We collected basic patient characteristic variables (age, gender), and initial ECG rhythm (ventricular fibrillation, [VF], pulseless electrical activity [PEA], asystole), existence of bystander CPR and witness. In calculating the time-to-ROSC (minutes from collapse to ROSC), we used the time of the first detection of collapse as a substitute for the time of collapse. Using the electronic medical record, we collected examination variables in the ED: existence of light reflex, spontaneous breathing, motor response (using Glasgow Coma Scale M scale; 1=no motor movement), and re-arrest in ED. These variables were checked by emergency physicians, and recorded immediately in the electronic medical record.

We defined primary outcome as days to extubation from admission day. In terms of weaning, patients' outcomes were designated as: received extubation, tracheostomy, or death in the intubated state. As variables of competing events to the primary outcome we also collected (1) the number of days from admission to tracheostomy and (2) the number of days to death in the intubated state. These two outcomes were not evaluated as they have the same probability of extubation compared to patients who received direct extubation, so we can't deal with these variables as censoring in COX regression model. In addition, we thought it was better to include information of length to tracheostomy or death, so we managed these two outcomes as competing events in Fine and Gray model analysis.

Protocol for targeted temperature management

In this study setting, prehospital care was delivered by emergency medical services. After being brought to hospital, patients were initially treated in the ED. Once the patient's condition was stabilized, they were admitted to the ICU. However, all patients suspected of cardiogenic etiology immediately received a cardiology catheter laboratory test, and percutaneous coronary intervention as needed before ICU admission. In SLIH, after OHCA patient's ROSC, emergency physicians judged whether patients should be introduced to TTM or not, based on information about their collapse situation, pre-hospital care, and outcomes of the physical or neurological examinations in the ED. TTM was introduced immediately after ROSC in the ED. For the treatment, physicians introduced intravenous cold saline, ice packs, gastric lavage, and a cooling blanket for temperature management. In the clinical course of cooling and for the following reasons these drugs would be used: sedation (midazolam, 0.1 to 0.15 mg/kg/h IV or propofol, 1 to 3 mg/kg/h IV), analgesia (fentanyl, 0.5 to 1 μg/kg/h IV), and neuro-muscular blockade (vecronium, 0.1 mg/kg/h IV). If needed clinically, physicians would utilize these drugs appropriately. Afterwards patients were passively rewarmed, at the rate of 0.5 to 1.0 °C over a 12-hour period. In order for physicians to examine neurological functions neuro-muscular blockades and sedation were discontinued. Fluid bolus, vasopressors and steroids were introduced for hemodynamic support as clinically indicated. In addition to these supports, intra-aortic balloon pump and pulmonary arterial catheter were introduced where physicians judged the necessity. After TTM was completed, emergency physicians conducted a neurological examination and when appropriate attempted to implement extubation as early as possible.

Statistical analysis

After characterizing the breakdown for each outcome variable (extubation, tracheostomy, and death in intubated state), they are analyzed using descriptive statistics. Continuous data were analyzed as means and standard deviations, or medians and interquartile ranges, according to the normality. We gave counts and percentages to categorical variables.

The causal relationship between days to extubation and variables of patient's characteristics, pre-hospital care, and examination in the ED were assessed with the COX regression model analysis for naïve model, setting days to tracheostomy and days to death in intubated state as censoring cases. Adjusting with those as confounding variables, we implemented multivariate analysis of Fine and Gray model as the final result. We defined that $p < 0.05$ was considered as statistically significant. Statistical analyses were performed using R commander version 2.4-1, and EZR provided by Kanda Y (2013).

Results

Characteristics of study subjects

Of the 113 eligible patients, 76 patients (67.2%) were extubated without a tracheostomy, 32 patients (28.3%) received tracheostomy and five patients (4.4%) died in-hospital being intubated without a tracheostomy. In these participants, two patients received reintubation within 48 hours after first extubation. Eventually, they were introduced tracheostomy. These cases were calculated as tracheostomy cases. Table 1 shows the baseline characteristics of these patients respectively. Majority gender was male, and a large part of patient’s first monitored rhythm was ventrilicular fibrillation. In Extubation group, 56 patients of total 76 patients received bystander CPR. This rate was bigger than tracheostomy and death group. About motor response in ED, 53 patients of total 76 patients showed motor response. Compared with that, only 8 patients of 32 patients in tracheostomy group showed motor response. The median of the primary outcome (days from admission to extubation) was 5.0 days, compared with competing risk variables: median days to tracheostomy was 7.5 days and median days to death was 9.0 days.

Cox regression analysis

Table 2 displays the results of the Cox regression analysis. Of these variables, the following variables were associated with earlier extubation: younger age; existence of bystander CPR; short time to ROSC; existence of motor response in ED.

Multivariate analysis

All candidate predictors were entered into the Fine and Gray multivariate analysis. Table 3 shows the results. In this Fine and Gray model analysis, four variables were retained as predictors, which had significant differences: younger age (95% CI of hazard ratio, 0.94 - 0.97); existence of bystander CPR (95% CI of hazard ratio, 1.13 - 3.23); short time to ROSC (95% CI of hazard ratio, 0.94 - 0.99); existence of motor response in ED (95% CI of hazard ratio, 1.37 - 3.94).

Discussion

Multivariate analysis revealed that a younger patient age, existence of bystander CPR, less time to ROSC, and finding a motor response in the ED indicated earlier extubation. To our knowledge, factors predicting earlier extubation after TTM was not known, although in a previous study Okada (2012) noted the predictive factors of neurological and survival outcome after TTM, and Martinell Louise (2017) reported predictors for a poor neurological outcome for OHCA patients as followed: Older age; longer duration of no flow; bilateral absence of corneal and pupillary reflexes; Glasgow Coma Scale motor response 1. Our study revealed that these factors could be beneficial not only for survival or neurological outcome, but also for early extubation after TTM. At last, the existence of a motor response in the ED was associated with early extubation. Compared to this, pupillary light reflex and spontaneous respiration did not show significant differences. This is an interesting point because in daily practice, we may not see which variable is the most significant factor. This finding may provide a novel approach for many physicians.

In their daily bedside practice, physicians aimed for early extubation, but the consensus of the medical team was not easily achievable because reintubation is associated with high mortality as Thille et al. (2011) reported. Thus, intensivists may judge the possibility of extubation based on the patient’s clinical course including the condition of pre-hospital care or the empirical findings while in the ED. In this study, eligible patients included only 2 cases of reintubation, and we didn’t collect other complication data associated with ventilation. Therefore, we couldn’t utilize this study result directly in terms of safety of extubation. However, there is possibility physicians could try earlier extubation from the fact almost all patients could be extubated with no complications. According to the results of this study, physicians can make an earlier judgement about extubation, early introduction of tracheostomy, and extubation oriented management during TTM. Additionally, physicians can make appropriate timing for ventilator weaning, and use of sedation or fluid during TTM toward earlier extubation because predictive variables can be obtained by the time of ICU admission.

Variable selection

Several articles discussed neurological and survival outcome, however we could not find a specific article, which mentioned the predictive factors for extubation after TTM. Therefore, we referred to studies of neurological and survival outcomes for variable selection. The variables included in this study can be obtained easily and during the early phase of the hospitalization, therefore these study results could be taken into account and utilize. Additionally, we tested the variance inflation factor of these variables to assure clinicians there were no significant multicollinearity in these variables.

Statistical analysis

In this study, we introduced Fine and Gray model analysis for investigate. Standard survival analysis deals with analyzing the time until the occurrence of the one event of interest. In the presence of more than one event of interest, standard method of estimating survival function (e.g. Cox regression method) may lead to bias estimate. As As Austin(2017) reported, Fine-Gray subdistribution hazard model is used for the analysis of time-to-event outcomes in the presence of competing events. Competing event is defined as events whose occurrence preclude the occurrence of the primary event of interest. In this study, clinical course after TTM is divided into three outcome events: extubation; tracheostomy; death in intubated state. As variables of competing events to the primary outcome extubation, we also collected the number of days from admission to tracheostomy and the number of days to death in the intubated state. And in statistical analysis, we dealt with days to tracheostomy and death as one combined competing event for stability of analysis because the number of patients who died in intubated state was very small.

Limitation

This study has several limitations. The first issue is about external validity. It is important to note that this is a single center observational investigation, and the sample size was relatively small. There was a risk of selection bias, because emergency physicians judge whether TTM should be introduced or not, and when patients can be extubated or whether physicians should do a tracheostomy. However, in this hospital, guidelines are followed in daily bedside practice. The international guidelines provide indications for TTM, and it has basically been followed in this hospital. To our knowledge, there is no gold standard protocol for extubation. Emergency physicians in this hospital usually require a spontaneous breathing test, and if that is successful they attempt the extubation if clinically possible. To sum up, the medical practice in this hospital doesn’t differ from other hospitals, so the influence of this limitation can be tolerated.

The second limitation is about potential confounders, which were not included in this study. This was an observational cohort study with an original approach. Therefore, we could have missed other potential confounders rather than the variables included in this study. That is important to note that physician's intention to extubation due to information of prehospital care and neurological finding in ED could be confounder which cannot be adjusted, because this was not blinded interventional study. However, physicians in this study didn't care specific information in advance of extubation, and judge whether extubate or not comprehensively according to patient's bed side information. In addition to that, this study revealed that basic information, which was obtained in the early phase of hospital contact, could be used to predict early extubation. These variables are assumed to be collected while providing standard hospital medical care, therefore the study results provide further convenience and versatility. This advantage overrides influence of potential confounders.

The third limitation is that patients who were excluded from the study were not evaluated. Sakamoto (2014) reported that patients who were treated with other TTM protocols or with extracorporeal life support could have gone through a different clinical course and most likely there would be a difference in prognosis. Additionally, we excluded patients whose cardiac arrest causes were non-cardiac etiology, because

OHCA patients with cardiac etiology are majority in patients who received TTM, and prognosis can be varied in perspective that patients with non-cardiac etiology tend to have less cardio pulmonary organs impaired. Though our result can't be applied to excluded patients, excluded patients were a relatively small sample, the results do apply to sizeable sample.

Final limitation is about management of death cases. In this study, death cases were only 5 patients, so we had to deal it as combined one competing event with tracheostomy. If we have larger number of death, it will be more desirable to manage death cases as independent competing event for precise estimate. But in this model, Cox regression model

Despite these disadvantages, we achieved meaningful results. In this study, all included cases could be followed through their entire hospitalization period, and this contributed to the robustness of this study's internal validity. In the future, a prospective multicenter study is needed for external validation.

Conclusion

Pre-hospital care and examinations on admission can predict early extubation after TTM. It could be helpful in clinical decision making around TTM.

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Fig. Flow diagram of patients through the study.

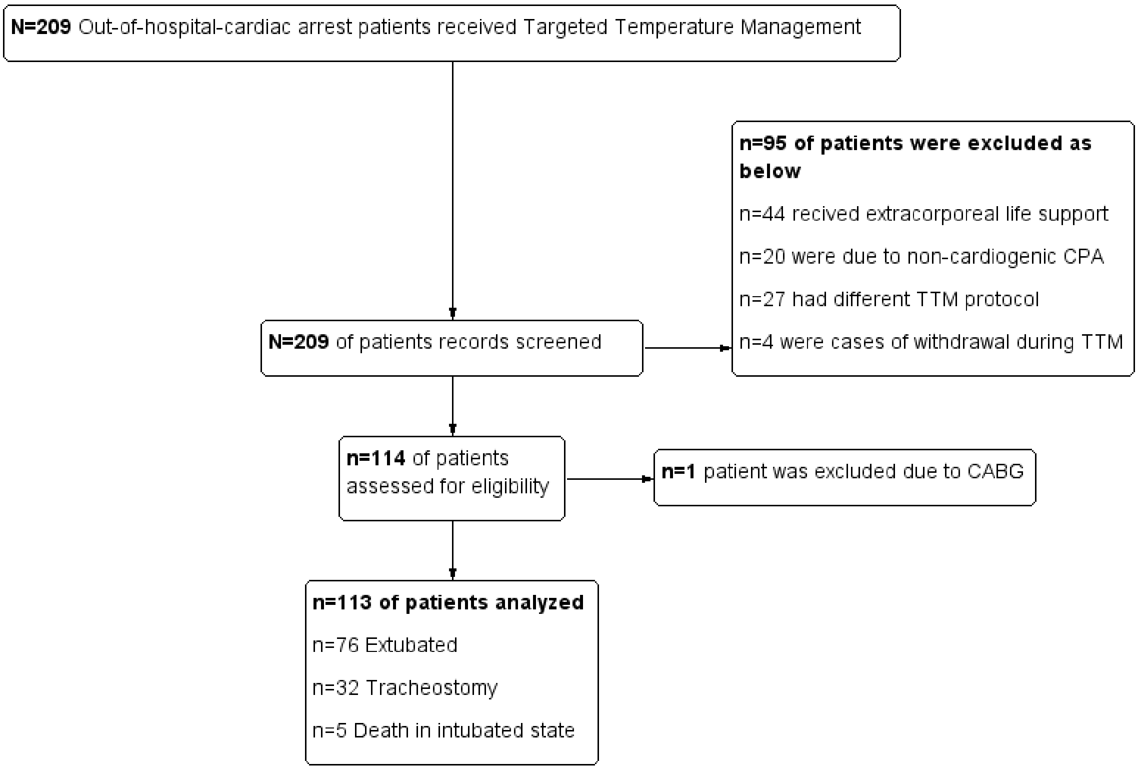

Table.1 Baseline characteristics of participants

		Number of patients			
		Total patients (N=113)	Extubation (n=76)	Tracheostomy (n=32)	Death in intubated state (n=5)
patients characteristics					
Age,median(IQR),y		59.0(18.0)	59.0(20.5)	61.5(15.3)	66.0(6.0)
Male gender		100	67	28	5
Prehospital care					
First monitored rhythm	VF	103	71	28	4
	PEA	5	3	1	1
	Asystol	5	2	3	0
Bystander CPR		72	56	12	4
Witness		92	61	26	5
TimetoROSC（Median,IQR),min		17.0(16.0)	15.0(7.3)	30.0(15.0)	38.0(30.0)
Neurological findings in ED					
Pupillary light reflex		76	58	17	1
Spontenous respiration		101	74	25	2
Motor response		61	53	8	0
RearrestER		10	5	4	1
Day to extubation, tracheostomy, or death in intubated state(IQR)		6.0(2.8)	5.0(2.0)	7.5(2.0)	9.0(4.0)

Table. 2 Result of Cox regression model analysis

	Hazard Ratio	95%CI	p value
Age, yr	0.96	0.94-0.97	<0.001*
Gender, male	1.06	0.51-2.20	0.87
First monitored rhythm: VF/VT or other	0.53	0.19-1.50	0.23
Bystander CPR	1.91	1.09-3.33	0.02*
Witness	0.79	0.43-1.48	0.47
Time to ROSC, min	0.96	0.93-0.99	0.005*
Pupillary light reflex	1.11	0.61-2.01	0.72
Spontanenous respiration	1.79	0.39- 8.17	0.45
Motor response	2.42	1.38-4.23	0.002*
Re-arrest	1.46	0.56-3.80	0.44

Table. 3 Result of Fine and Gray model multivariate analysis

	Hazard Ratio	95%CI	p value
Age, yr	0.96	0.94-0.97	<0.001*
Gender, male	1.1	0.66-1.86	0.7
First monitored rhythm: VF/VT or other	0.59	0.29-1.19	0.14
Bystander CPR	2.05	1.20-3.50	0.008*
Witness	0.78	0.49-1.26	0.31
Time to ROSC, min	0.96	0.93-0.99	0.003*
Pupillary light reflex	1.1	0.65-1.89	0.72
Spontanenous respiration	2.07	0.42-10.1	0.37
Motor response	2.39	1.39-4.14	0.002*
Re-arrest	1.51	0.76-3.01	0.24