Predicting Time to Death after Terminal Withdrawal of Mechanical Ventilation

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A thesis

submitted in partial fulfillment of the

requirements for the degree of:

Master of Science

University of Washington

2014

Committee:

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Program Authorized to Offer Degree:

Public Health - Epidemiology

University of Washington

Abstract

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Discussions about withdrawal of life-sustaining therapies often include family members of critically ill patients. These conversations should address essential components of the dying process, including expected time to death after withdrawal. Identification of predictors of time to death after terminal withdrawal of mechanical ventilation may aid physician communication about the dying process. We conducted an observational analysis from a single-center, before-after evaluation of an intervention to improve end-of-life care. We studied 330 patients who died after terminal withdrawal of mechanical ventilation. Predictors included patient demographics, laboratory variables, respiratory variables, physiologic variables, and medication use. The median (IQR) time to death for the entire cohort was 0.58 hours (0.22-2.25 hours) after withdrawal of mechanical ventilation. Using Cox regression, independent predictors of shorter time to death included positive end-expiratory pressure (per-1 cm H2O increase hazard ratio [HR], 1.07; 95% CI, 1.04-1.11), static pressure (per-1 cm H2O HR, 1.02; 95% CI 1.01-1.04), male sex (HR, 1.28; 95% CI 1.00-1.65), and presence of diabetes (HR, 1.57; 95% CI 1.14-2.18). Non-invasive mean arterial pressure predicted longer time to death (per-1 mmHg HR, 0.98; 95% CI 0.97-0.99). Patient sex, comorbid illness, and physiologic parameters may inform physician predictions of time to death after withdrawal and facilitate communication with family members of dying patients.

INTRODUCTION

Death is common in the intensive care unit (ICU) and is frequently preceded by the withdrawal of life-sustaining therapies [1-3]. Discussions surrounding withdrawal of life-sustaining therapies often include family members of critically ill patients, and experts in end-of-life care recommend that these conversations address essential components of the dying process, including expected time to death [4,5]. Though physicians are encouraged to address expected time to death after withdrawal of life-sustaining measures, the dying process may vary significantly from patient to patient and may be influenced by a number of clinical variables. Studies evaluating time to death after terminal withdrawal of life-sustaining measures suggest that 45-76% of deaths will occur within 60 minutes [6-13] and the majority of patients will die within 24 hours [14]. However, residual uncertainty in predicting time to death may discourage routine discussion of this important issue during family conferences. Most studies evaluating time to death after withdrawal of life-sustaining measures have assessed time to death as a dichotomous outcome (death within 60 minutes) and evaluated a limited number of physiologic variables. Utilization of time to death in a continuous fashion with assessment of a broader array of clinical parameters may better identify independent predictors of time to death after withdrawal of life-sustaining measures. Improved predictive capability may enhance communication with family members about the dying process and thus improve end-of-life care for patients and their family members.

Utilizing data from a single-center study of a quality improvement intervention to enhance palliative care in the ICU [15], we identified individuals receiving invasive mechanical ventilation who underwent withdrawal of life-sustaining measures prior to death. We examined associations between a variety of demographic, laboratory, respiratory, or physiologic variables and time to death assessed as a continuous

outcome. In addition, we evaluated associations between administered medications, including vasopressors/inotropes and analgesics or sedatives, and time to death after terminal withdrawal of mechanical ventilation. We hypothesized that markers of severity of illness would serve as independent predictors of shorter time to death but medications provided prior to withdrawal for sedation or analgesia would not reliably predict time to death.

METHODS

Participants and Setting

Data for this study were drawn from a single-center, before–after evaluation of a multifaceted intervention designed to improve ICU clinicians' ability to provide palliative and end-of-life care to critically ill patients and their family members [15]. Eligible patients were those who had died in an ICU after a minimum stay of 6 hours before death or who had died within 24 hours after being transferred to another hospital location from the ICU. These patients were identified by examining hospital admission, discharge, and/or transfer records daily during two time periods: before the intervention (July 2003 to March 2004) and after the intervention (December 2004 to October 2005). Patients who were in the ICU for less than 6 hours or who died more than 24 hours after transfer out of the ICU were excluded. The study included 590 patients (pre-intervention, n=253; post-intervention, n=337) receiving care in a university-based, inner-city level I trauma center. The intervention was aimed at clinicians and hospitals and focused on changing physician behavior via five components: 1) clinician education about palliative care in the ICU; 2) identification and training of ICU clinician local champions for palliative care; 3) academic detailing of nurse and physician ICU directors to address individual ICU-specific barriers to improving end-of-life care; 4) feedback of individual ICU-specific

quality data; and 5) implementation of system supports. The intervention did not affect the outcome of interest in this observational analysis. For our analysis, we excluded patients who died in the setting of full support, who were not receiving invasive mechanical ventilation prior to withdrawal of life support, or who experienced brain death. All patients underwent terminal withdrawal of mechanical ventilation. Following exclusion of ineligible patients, 330 individuals remained in the final sample. The University of Washington Human Subjects Division approved all study procedures.

Data Collection and Variables

Retrospective medical record review was completed in two phases. The initial abstraction was completed during the before-after study by trained chart abstractors using a standardized chart abstraction protocol. Information about the time of withdrawal as well as data on patient demographics was collected from medical records. Additional medical record abstraction for this analysis was completed by researchers who utilized similar chart abstraction protocols, training, and reliability reviews (Appendix A). Co-review of randomly selected charts resulted in > 90% agreement on all items (Appendix B). During the second phase of abstraction additional clinical variables, lab data, and medication details were obtained.

Outcome variables: For this investigation the outcome of interest was time to death after terminal withdrawal of mechanical ventilation in the ICU, calculated from the recorded time of discontinuation of mechanical ventilation to death in hours. Terminal withdrawal was defined as the episode of withdrawal of ventilator support most proximal to death, with documentation in the medical record endorsing the expectation that the patient would die without ventilation. Of the 330 patients included in this study, 8 died during the process of withdrawal of life-sustaining therapies and prior to complete cessation of

mechanical ventilation, resulting in a time to death of zero. Because these patients represent an important population undergoing withdrawal of life-support, each was assigned a time to death of 1 sec so that they might be included in the analysis.

Predictor variables: We evaluated multiple predictors of time to death after withdrawal of mechanical ventilation, including patient demographics, laboratory variables, respiratory care variables, physiologic variables, and medication use. Patient-level characteristics were recorded during the parent study and included patient age (in years), gender (male/female), race/ethnicity (Non-Hispanic white/Other), insurance status (Private insurance or Medicare/Other) and medical comorbidities. Comorbidities were based on identification of the condition in the medical record and include the following: diabetes, chronic respiratory disease, congestive heart failure, malignancy, or cerebrovascular disease. Laboratory values abstracted for this analysis were the most recent value obtained within 24 hours of ventilator discontinuation and included: pH from arterial blood gas, partial pressure of oxygen from arterial blood gas (PaO2, mmHg), lowest serum bicarbonate (mEq/L), highest serum creatinine (mg/dL), and lowest platelet count (10^9/L). We also recorded the presence or absence of a documented arterial lactate within the 24 hours prior to death. Respiratory care variables were the most recent value obtained within 24 hours of ventilator discontinuation but prior to ventilator wean and included: inspired fraction of oxygen (FiO2 %), positive end-expiratory pressure (PEEP cm H2O), static pressure (cm H2O), tidal volume per predicted body weight (ml/kg), and minute ventilation (ml/min). We also obtained information regarding the performance of a spontaneous breathing trial within the 24 hours prior to withdrawal. Neurologic status was assessed via the lowest recorded Glasgow Coma Scale score (range 2-15) [16] within the 24 hours prior to withdrawal. For hemodynamic status we recorded the lowest sustained mean arterial pressure (MAP), defined as the two lowest MAP values that

were documented for > 30 minutes during the 24 hours prior to ventilator discontinuation and then averaged those values for a final estimate. We included medications that might be associated with time to death after withdrawal of mechanical ventilation, including vasoactive agents, sedatives, and analgesics. These medications were abstracted from nursing flow sheets and the medication administration record, using the 24 hour time period prior to death. Vasopressors or inotropes (Norepinephrine, Dopamine, Dobutamine, Epinephrine, Vasopressin, and Phenylephrine) were categorized according to the number of agents a patient received during the 24 hours prior to ventilator withdrawal. Receipt of sedatives and/or analgesics (opiates, benzodiazepines, and propofol) in the 24 hours prior to death was also recorded for each medication group (Yes/No).

Data Analysis

We used Kaplan-Meier survival plots to describe time to death for this group of patients. Time to death was not a normally distributed variable, thus comparisons of median time to death by patient demographics and comorbidities were performed using the non-parametric Wilcoxon rank-sum test or Kruskal-Wallis equality of proportions rank test as appropriate. We used Cox proportional hazards regression to examine the relationship of the survival distribution to the covariates of interest and identify independent predictors of time to death. A hazard ratio > 1.0 represents a covariate associated with a shorter time to death (i.e. an increased risk of death) whereas a hazard ratio < 1.0 suggests a longer time to death (i.e. decreased risk of death). We evaluated the association between our predictors and time to death in unadjusted models then constructed separate regression models for each predictor adjusted for patient age, race/ethnicity, sex, and insurance status. In order to determine the best predictors in this set of variables, we used a backward stepwise regression procedure

with *P*=0.2 as the significance level for removal and determined the covariates to be included in a final multivariate model that also retained patient age, race/ethnicity, sex, and insurance status. Analyses were performed using STATA 13.0 (College Station, TX) with statistical significance for all hypothesis tests set at *P*<0.05.

RESULTS

Baseline characteristics of the 330 individuals included in the cohort are described by patient gender in Table 1. Mean patient age was 61 years (SD 17) and 64% of patients (n=211) were male. The majority of patients were white, non-Hispanic (79%), and most had private insurance or Medicare (72%). Diabetes mellitus and chronic respiratory disease were the most common comorbidities. Most patients were admitted to the hospital from home (45%) or acute care facilities (43%), and the majority of patients were admitted to the ICU from the emergency department (75%). Average length of stay in the ICU was 6.7 days (SD 8.3). Clinical variables and medication utilization are described in Table 2. The median (IQR) time to death for the entire cohort was 0.58 hours (0.22-2.25 hours) after withdrawal of mechanical ventilation, with a range of 0 to 76 hours (Figure 1). Median time to death for those surviving more than 1 hour (n=133) was 3 hours.

Unadjusted associations between time to death after withdrawal and patient demographics and comorbidities

Patient gender was associated with a significant difference in median time to death after withdrawal of mechanical ventilation. Men had shorter times to death than women (0.42 versus 0.83 hours, respectively, P=0.001). Neither race/ethnicity nor insurance type was associated with time to death after withdrawal. Among the evaluated comorbidities,

diabetes mellitus was associated with shorter time to death whereas patients with cerebrovascular disease experienced a longer time to death after withdrawal (Table 3).

Clinical predictors of time to death after withdrawal

In unadjusted analyses, higher pH, bicarbonate level, and platelet count were all associated with a longer time to death. Higher creatinine was associated with a shorter time to death as was documentation of arterial lactic acid in the 24 hours prior to withdrawal. Among the respiratory variables, higher FiO2, PEEP, minute ventilation and static pressures were associated with shorter time to death and receipt of higher tidal volumes was associated with a longer time to death. Patients with higher GCS scores and MAPs were more likely to live longer after withdrawal. Medication administration was associated with time to death where those receiving more than one vasopressor or inotrope in the 24 hour period prior to withdrawal had shorter times to death. However, sedative or analgesic administration was not associated with time to death. After adjusting for patient age, race/ethnicity, sex, and insurance type, these associations remained similar. In addition, after adjustment for demographic variables, the presence of a spontaneous breathing trial in the 24 hours preceding withdrawal was associated with a longer time to death (Table 4).

Results from a final multivariate model are provided in Table 5. Covariates included in the final model did not demonstrate evidence of violation of the proportional hazards assumption. Patient age, race/ethnicity, sex, and insurance type were retained in this model *a priori* and the remaining covariates were identified via a backward stepwise regression procedure using P=0.2. In our final model, male sex and diabetes were identified as predictors of shorter time to death. Of the respiratory variables remaining in the final model, higher PEEP and higher static pressure prior to withdrawal

were associated with shorter time to death. Higher noninvasive MAP was associated with a longer time to death.

DISCUSSION

In this observational analysis of 330 patients undergoing terminal withdrawal of mechanical ventilation in the ICU, the majority of patients died within one hour of withdrawal (60%) and the remainder within 24 hours (98%). Most studies assessing time to death after terminal withdrawal of mechanical ventilation have utilized a dichotomous outcome, with death occurring in 60 minutes compared to death occurring after this time. The assessment of time to death as a continuous variable avoids creation of an arbitrary cut-point and allows more effective use of patient data, and we were able to identify several predictors of time to death using this approach. Male sex and diabetes were associated with shorter time to death as were variables reflective of severe respiratory dysfunction (higher PEEP and higher static pressures). Conversely, higher mean arterial pressure was associated with a longer time to death. Administration of sedatives or analgesics in the 24 period prior to withdrawal was not associated with time to death.

Previous studies have demonstrated an association between markers of significant respiratory impairment and time to death after terminal withdrawal of mechanical ventilation, with both FiO2 and PEEP identified as independent predictors of shorter time to death [12,13,17]. Other measures of respiratory function have also been assessed as predictors of time to death, including an oxygenation index (OI) calculated using the FiO2, mean airway pressure, and PaO2. Higher OI values are indicative of worse oxygenation and have been associated with shorter time to death [8-10]. In our study both higher PEEP and higher static pressures in the time period most proximal to ventilator withdrawal were predictive of shorter time to death. This finding makes sense

from a physiologic perspective, given the likelihood for more rapid deterioration in oxygenation and subsequent tissue hypoxia in patients requiring more support from mechanical ventilation prior to withdrawal. Our findings, in conjunction with prior studies, suggest that markers of respiratory dysfunction should be considered key components of physician predictions of time to death after withdrawal of mechanical ventilation. The creation of a composite measure of respiratory dysfunction that incorporates factors such as FiO2, PEEP, and static pressures may serve as a valuable tool to aid physicians discussing terminal withdrawal of mechanical ventilation with family members of critically ill patients. Importantly, such a tool would assist in communication about the dying process, an essential component of high quality end-of-life care [18,19]. Blood pressure parameters have also been associated with time to death, with higher systolic blood pressure identified as a predictor of longer time to death [12]. Higher non-invasive mean arterial pressure was similarly associated with longer time to death. This too is biologically plausible given the likelihood that lower MAP would reflect a greater severity of illness and provide the patient with less hemodynamic reserve upon initiation of the withdrawal process.

Shorter time to death observed for men may reflect existing gender differences in end-of-life care. Women express more favorable attitudes regarding hospice care than men [20], are less likely than men to receive intensive life-sustaining treatments at the end of life, and are more likely to utilize hospice services prior to death [21-23]. On the other hand, men are more likely than women to report a positive view of life-sustaining therapies [24]. These differences may reflect personal preferences, and preferences for less intensive life-sustaining treatments among women may influence the timing of decisions to pursue withdrawal of life-sustaining therapies. Earlier decisions to withdraw mechanical ventilation could result in longer time to death if multi-organ failure or lung

injury were not as severe. Alternatively, men may possess a higher severity of illness at the time of ICU admission which may not be fully captured by the available data and may thus die more rapidly than women after withdrawal of mechanical ventilation. Shorter time to death for men has been previously observed and may serve as an important consideration for prediction purposes [14].

The association between shorter time to death and a history of diabetes is interesting, and there are several potential explanations for this association that relate to the pathophysiology of this chronic condition. Diabetes is a systemic process with the potential to affect end-organ function in myriad ways, and individuals with diabetes frequently experience both microvascular and macrovascular complications of chronic hyperglycemia [25]. This preexisting vascular injury may promote more rapid death for patients undergoing terminal withdrawal of mechanical ventilation by priming patients for cardiac ischemia and arrhythmia. Specifically, the cardiac autonomic neuropathy that may be present in diabetic patients could facilitate more sudden hemodynamic collapse after withdrawal. Though there are plausible explanations for this finding, the association between diabetes and shorter time to death after terminal withdrawal of mechanical ventilation has not been well-described and thus warrants additional investigation.

Our study has multiple strengths including a large sample size, diverse ICU population, the variety of laboratory and physiologic variables assessed, and a high rate of reliability of abstracted data. Most studies of time to death after withdrawal of life-sustaining measures include fewer than 200 patients, and here we assessed 330 individuals undergoing terminal withdrawal of mechanical ventilation. Many of these studies occur in the neurocritical care setting, and our investigation included a mixed medical and surgical patient population. Inclusion of several laboratory values such as bicarbonate, creatinine, and platelet count is also unique as is the evaluation of several

different respiratory parameters including tidal volume and performance of a spontaneous breathing trial. Finally, the use of Cox regression, as compared to creation of a binary outcome and use of logistic regression, is often preferred when performing a time to event analysis and has not been routinely done in other studies assessing time to death after terminal withdrawal.

This study has several important limitations. First, data from this study was captured from a university-based, inner-city level I trauma center and may not be generalizable to other settings. However, the duration of survival following terminal withdrawal of mechanical ventilation is similar to that seen in numerous other studies and identified predictors are either similar to those seen in those investigations or biologically plausible if not studied previously. Second, there was missing data for several of our predictors of interest. Though missingness was addressed by including a category to represent the missing cases where possible and thus retain these individuals in regression analyses, missing data for continuous variables may lead to biased estimates. Finally, we could not account for all potential variables that might reflect severity of illness and thus may not have captured other important predictors of time to death.

For family members of dying patients, assurance that the patient will not be abandoned during the process of withdrawal of life-sustaining measures and that pain and suffering will be minimized is essential. In addition to this, providing insight into the duration of the dying process is also important to allow families time to prepare for the patient's death and to include those individuals who would like to be present during the dying process. By integrating identified predictors of time to death into the discussion surrounding withdrawal of mechanical ventilation, physicians may be more comfortable

providing estimates of time to death and in doing so assist family members in coping with the death of a loved one.

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Figure 1. Kaplan-Meier estimate of survival after withdrawal of mechanical ventilation.

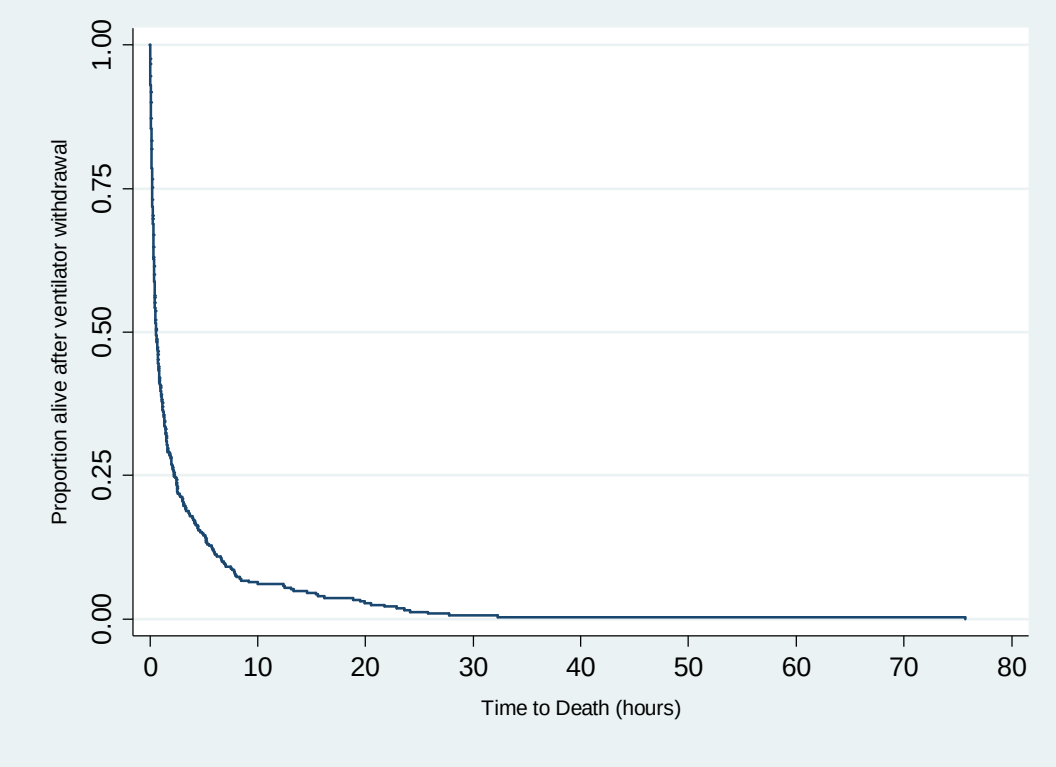

Table 1. Patient demographics, comorbidities, and hospitalization information by gender

	Female (n=119)	Male (n=211)
Age, mean years (SD)	63 (15.4)	60 (18.2)
Race, n (%)		
White, non-Hispanic	95 (80)	167 (79)
Other race/ethnicity	19 (16)	33 (16)
Missing	5 (4)	11 (5)
Insurance type, n (%)		
Private or Medicare	92 (77)	144 (68)
Other	27 (23)	67 (32)
Comorbidities, n (%)		
Diabetes	19 (16)	45 (21)
Chronic respiratory disease	19 (16)	39 (18)
Congestive heart failure	10 (8)	30 (14)
Malignancy	14 (12)	26 (12)
Cerebrovascular disease	14 (12)	20 (9)
Hospital admission source, n (%)		
Home	50 (42)	97 (46)
Acute care facility	62 (52)	79 (37)
Skilled nursing facility	3 (3)	15 (7)
Homeless	1 (1)	8 (4)
Group home	2 (2)	5 (2)
Office/clinic	0 (0)	4 (2)
Rehab	0 (0)	2 (1)
Missing	1 (1)	1 (1)
ICU admission source, n (%)		
Emergency department	95 (80)	152 (72)
Hospital floor/observation unit	16 (13)	38 (18)
Operating room/procedure recovery	7 (6)	19 (9)
Direct admission	1 (1)	2 (1)
Discharge service, n (%)		
Medicine	56 (47)	114 (54)
Surgery	63 (53)	97 (46)
ICU LOS, mean days (SD)	6.5 (7.2)	6.8 (8.9)

ICU *Intensive care unit* LOS *Length of stay.*

Table 2. Clinical variables and medication utilization from the 24 hour time period prior to withdrawal of mechanical ventilation

	Total N=330		
	n	Missing, n (%)	% or mean (SD)
Laboratory variables			
pH, %		26 (8)	
Less than 7.4	114	-	35
≥ 7.4	190	-	58
Arterial PaO2 (mmHg), mean (SD)	304	26 (8)	119 (73)
Serum bicarbonate (mEq/L), mean (SD)	312	18 (5)	22 (6)
Creatinine (mg/dL), mean (SD)	312	18 (5)	1.7 (2)
Arterial lactic acid within 24 hours, %		0 (0)	
No	227	-	69
Yes	103	-	31
Platelets (10^9/L)	306	24	190 (118)
Respiratory variables			
FiO2 (%, from ventilator), mean (SD)	322	8 (2)	54 (24)
PEEP (cm H2O), mean (SD)	318	12 (4)	7 (4)
Static pressure (cm H2O), mean (SD)	297	33 (10)	26 (9)
Tidal volume per predicted body weight (ml/kg), %		71 (22)	
< 6.5	81	-	25
6.5-9	71	-	22
> 9	107	-	32
Minute ventilation (ml/min), mean (SD)	312	18 (5)	11 (4)
Spontaneous breathing trial, %		8 (2)	
No	278	-	84
Yes	44	-	13
Physiologic variables, mean (SD)			
Glasgow Coma Scale (2-15)	321	9 (3)	4 (2)
Noninvasive MAP (mmHg)	321	9 (3)	73 (15)
Medications within 24 hours prior to withdrawal, %			
Vasopressors and/or Inotropes		2 (1)	
None	211	-	64
One	81	-	25
More than one	36	-	11
Opioids		2 (1)	
No	120	-	37
Yes	208	-	63
Benzodiazepines		2 (1)	
No	85	-	26
Yes	243	-	74
Propofol		2 (1)	
No	270	-	82
Yes	58	-	18

PaO2 *Partial pressure of oxygen* FiO2 *Fraction of inspired oxygen* PEEP *Positive end-expiratory pressure* MAP *Mean arterial pressure*

Table 3. Unadjusted associations between median time to death after withdrawal of mechanical ventilation and patient demographics and comorbidities[a]

		Time to Death, hours		
	n	Median	IQR	*P* value
Age, years				0.051
≤ 50	81	0.48	0.17-2.3	
51-60	70	1.28	0.33-4.9	
61-70	56	0.57	0.22-2.7	
71-80	79	0.50	0.17-1.5	
> 80	44	0.47	0.24-1.4	
Sex				**0.001**
Female	119	0.83	0.37-3.1	
Male	211	0.42	0.17-2.0	
Race/ethnicity				0.25
White, non-Hispanic	262	0.67	0.20-2.3	
Other race/ethnicity	52	0.38	0.22-1.7	
Insurance type				0.48
Private or Medicare	236	0.53	0.20-2.3	
Other	94	0.66	0.25-2.2	
Diabetes				**0.035**
No	266	0.68	0.22-2.6	
Yes	64	0.47	0.18-1.0	
Chronic respiratory disease				0.48
No	272	0.52	0.20-2.3	
Yes	58	0.74	0.25-2.2	
Congestive heart failure				0.55
No	290	0.58	0.22-2.4	
Yes	40	0.63	0.23-1.2	
Malignancy				0.96
No	290	0.55	0.22-2.3	
Yes	40	0.68	0.23-2.0	
Cerebrovascular disease				**0.045**
No	296	0.51	0.2-2.1	
Yes	34	1.43	0.5-2.5	

a. Time to death after withdrawal was not a normally distributed variable, thus non-parametric Wilcoxon rank-sum test or Kruskal-Wallis equality-of-populations rank test were used as appropriate.

Table 4. Predictors of time to death after terminal withdrawal of mechanical ventilation, adjusted for demographic variables[a]

		Unadjusted			*Adjusted for Age, Sex, Race, Insurance*		
	n[b]	Hazard Ratio	95% CI	*P* value	Hazard Ratio	95% CI	*P* value
Laboratory variables							
pH							
Less than 7.4	114	1.00	Referent		1.00	Referent	
≥ 7.4	190	0.60	0.48-0.76	**< 0.001**	0.58	0.45-0.74	**< 0.001**
Arterial PaO2 (mmHg)	304	1.00	1.00-1.00	0.18	1.00	1.00-1.00	0.19
Serum bicarbonate (mEq/L)	312	0.96	0.93-0.98	**< 0.001**	0.96	0.94-0.98	**<0.001**
Creatinine (mg/dL)	312	1.09	1.02-1.17	**0.010**	1.08	1.01-1.16	**0.035**
Arterial lactic acid within 24 hrs							
No	227	1.00	Referent		1.00	Referent	
Yes	103	1.61	1.27-2.04	**< 0.001**	1.60	1.26-2.04	**< 0.001**
Platelets (10^9/L)	306	1.00	1.00-1.00	**0.001**	1.00	1.00-1.00	**0.001**
Respiratory variables							
FiO2 (%, from ventilator)	322	1.01	1.01-1.02	**< 0.001**	1.01	1.01-1.02	**< 0.001**
PEEP (cm H2O)	318	1.10	1.07-1.13	**< 0.001**	1.10	1.07-1.13	**< 0.001**
Static pressure (cm H2O)	297	1.04	1.02-1.05	**< 0.001**	1.04	1.03-1.05	**< 0.001**
Tidal volume per PBW (ml/kg)							
< 6.5	81	1.00	Referent		1.00	Referent	
6.5-9	71	0.75	0.54-1.03	0.076	0.75	0.54-1.03	0.075
> 9	107	0.70	0.52-0.94	**0.018**	0.71	0.52-0.96	**0.024**
Minute ventilation (ml/min)	312	1.06	1.03-1.09	**< 0.001**	1.06	1.02-1.09	**0.001**
Spontaneous breathing trial							
No	278	1.00	Referent		1.00	Referent	
Yes	44	0.73	0.53-1.01	0.056	0.72	0.52-0.99	**0.043**
Physiologic variables							
Glasgow Coma Scale (2-15)	321	0.94	0.89-1.00	0.054	0.93	0.88-0.99	**0.025**
Noninvasive MAP (mmHg)	321	0.98	0.97-0.99	**< 0.001**	0.98	0.97-0.99	**< 0.001**
Medications within 24 hours							
Vasopressors and/or Inotropes							
None	211	1.00	Referent		1.00	Referent	
One	81	1.52	1.18-1.97	**0.001**	1.47	1.14-1.91	**0.003**
More than one	36	2.94	2.04-4.25	**< 0.001**	2.84	1.97-4.11	**< 0.001**
Opioids							
No	120	1.00	Referent		1.00	Referent	
Yes	208	0.94	0.75-1.18	0.60	0.95	0.76-1.20	0.67
Benzodiazepines							
No	85	1.00	Referent		1.00	Referent	
Yes	243	1.21	0.94-1.55	0.13	1.27	0.99-1.64	0.064
Propofol							
No	270	1.00	Referent		1.00	Referent	
Yes	58	0.92	0.69-1.22	0.55	0.95	0.71-1.26	0.71

PaO2 *Partial pressure of oxygen* FiO2 *Fraction of inspired oxygen* PEEP *Positive end-expiratory pressure* PBW *Predicted body weight* MAP *Mean arterial pressure*

a. Estimates for time to death after terminal withdrawal of mechanical ventilation from Cox proportional hazards regression.

b. For categorical variables missing data were included as a separate category, not shown here.

Table 5. Multivariable stepwise model of predictors of time to death after terminal withdrawal of mechanical ventilation[a]

	n[b]	Hazard Ratio	95% CI	*P* value
Age, years	330	1.00	1.00-1.01	0.30
Sex				
Female	119	Referent	1.00	
Male	211	1.28	1.00-1.65	**0.049**
Race				
White, non-Hispanic	262	Referent	1.00	
Other race/ethnicity	52	1.32	0.95-1.84	0.098
Insurance type				
Other	94	Referent	1.00	
Private or Medicare	236	1.07	0.79-1.45	0.65
Diabetes				
No	266	Referent	1.00	
Yes	64	1.57	1.14-2.18	**0.006**
Cerebrovascular disease				
No	296	Referent	1.00	
Yes	34	0.78	0.52-1.16	0.23
pH				
Less than 7.4	114	Referent	1.00	
≥ 7.4	190	0.95	0.68-1.32	0.76
PEEP (cm H2O)	318	1.07	1.04-1.11	< **0.001**
Static pressure (cm H2O)	297	1.02	1.01-1.04	**0.005**
Tidal volume per PBW (ml/kg)				
< 6.5	81	Referent	1.00	
6.5-9	71	1.02	0.73-1.42	0.92
> 9	107	1.13	0.81-1.57	0.46
Noninvasive MAP (mmHg)	321	0.98	0.97-0.99	< **0.001**
Opioids				
No	120	Referent	1.00	
Yes	208	1.13	0.85-1.51	0.39
Benzodiazepines				
No	85	Referent	1.00	
Yes	243	1.19	0.86-1.63	0.30
Propofol				
No	270	Referent	1.00	
Yes	58	0.88	0.64-1.20	0.41

PEEP *Positive end-expiratory pressure* PBW *Predicted body weight* MAP *Mean arterial pressure*

a. Estimates for time to death after terminal withdrawal of mechanical ventilation from multivariate Cox proportional hazards regression. Variables selected for this model via backward stepwise regression with P=0.2. Variables removed from this model included: Minute ventilation, Congestive heart failure, Creatinine, Bicarbonate, Fraction of inspired oxygen, Glasgow coma scale, Vasopressors/inotropes, Lactic acid measurement, Malignancy, Spontaneous breathing trial, Arterial partial pressure of oxygen, Platelet count, and Chronic respiratory disease.

b. For categorical variables missing data for each variable were included in the final model as separate categories, not shown here. Final model n=295.

Appendix A

Chart Abstraction

Demographic Data

Where to look: take this from the master patient list

Patient identification number (PID): Be very careful to enter the correct PID for the patient

Date and time of withdrawal of ventilator: take this from the master patient list.

Variables = VentDt and VentTM

Rules: record the withdrawal time in military format (00:00-23:59)

*Check the medical record for accuracy of the date and time reported on the master patient list. RT notes used preferentially, supplemented by nursing notes as needed.

Laboratory Data

Where to look: take this information from the 'LAB' section on ORCA. It will automatically bring up the last 250 results. If there is a result missing you can press the right-most arrow on the blue tab titled 'last 250 results' to get more results.

Rules:

1. If values are outside of the expected values then star the value and make a note of it on the patient tracking form under 'NOTES.'

2. If the value is within 24 hours of ventilator discontinuation then check the box 'w/in 24 hrs.'

3. If the value is not within 24 hours of ventilator discontinuation then record the most recent value and the date of the value, only if it occurs within 1 week of ventilator discontinuation.

4. If no value occurring within this time frame (within 24 hours or 1 week of ventilator discontinuation) can be identified, mark this value as absent by striking through the data item on the form.

FIO2 (fraction of inhaled oxygen) - record the FIO2 at the exact time of the most recent arterial blood gas (ABG) prior to ventilator discontinuation.

Where to look*:* take this from the FIO2, ART of the ABG

Rules:

Verify the FIO2 by looking at the documented 'O2 FLOW' on the 'RESPIRATORY CARE INPATIENT RECORD' at the exact time of the ABG.

If there is no O2 FLOW recorded for the time of the ABG, then look at 'O2 ADMINISTRATION' under the 'VITAL SIGNS FLOW SHEET' at the exact time of the ABG.

Expected values: 21-100% oxygen

pH - record the most recent value within the 24 hours prior to ventilator discontinuation.

Where to look: take these from the most recent arterial blood gas (ABG) under 'LAB'.

Expected values: 6.80 - 7.70

pO2 (partial pressure of oxygen) - record the most recent value within the 24 hours prior to ventilator discontinuation.

Where to look: take this from the most recent arterial blood gas (ABG) under 'LAB'.

Expected values: 40 - 400 mm Hg

NOTE from 4/9/12 - If recorded values are < 40, recode as *missing* value. Rationale: assuming that this was really a venous blood gas value, not an arterial blood gas value.

Venous fractional oxygen saturation (aka mixed venous oxygen saturation/SvO2) - record the most recent SvO2 within the 24 hours prior to ventilator discontinuation.

Where to look: Take this from the VENOUS blood gas under 'LAB'

Expected values: 50 - 90 %

CO2 (bicarbonate) - record the lowest value within the 24 hours prior to ventilator discontinuation.

Where to look: take this from the most recent blood electrolytes under 'LAB'

Expected values: 5 - 45 mEq/L

Creatinine - record the highest value within the 24 hours prior to ventilator discontinuation.

Where to look: take this from the most recent blood electrolytes under 'LAB'

Expected values: 0.4 - 8.0

L-lactate - record the highest value for the arterial lactate within the 24 hours prior to ventilator discontinuation.

Where to look: take this from 'MISC CHEMISTRIES' under 'LAB'.

Rules:

If no arterial lactate then record most recent venous lactate and mark with a V (ex. V 4.5)

Expected values: 0 - 35.0 mmol/L

Bilirubin - record the highest total bilirubin value within the 24 hours prior to ventilator discontinuation.

Where to look*:* take this from the most recent liver studies under 'LAB'

Platelets - record the lowest value within the 24 hours prior to ventilator discontinuation.

Where to look: take this from the most recent CBC under 'LAB'

Ventilator parameters

Where to look: take this information from the 'Respiratory Care Inpatient Record' which is located under 'Inpatient Documents'

Rules:

1. Use the most recent ventilator numbers prior to initiation of ventilator weaning protocol. This will be at a FIO2 > 21% that is stable over 2 time periods.

2. If an isolated value is missing (for example TV/PBW) you may substitute that value from the documented ventilator values immediately before or after the missing value.

FIO2 (fraction of inhaled oxygen) - record the most recent FIO2 documented for more than a 1 hour period of time prior to ventilator discontinuation.

Rules:

1. Occasionally there is a misdocumented or isolated increase in FIO2. Record a value only if it has been documented for more than a 1 hour period of time.

2. Look at the 'VITAL SIGNS FLOW SHEET' to confirm FIO2.

Expected values: 21 - 100%

PEEP (positive expiratory end pressure) - record the most recent PEEP prior to ventilator discontinuation.

Expected values: 5 - 18 cm H2O

Static pressure - record the most recent value prior to ventilator discontinuation.

Expected values: 20 - 50 cmH2O

NOTE from 4/9/12 - If values > 50 are found, recode to 50. Randy and Sarah suggested that this would be acceptable, as long as it is clear that these are what the RT intended to enter.

Static compliance - record the most recent value prior to ventilator discontinuation.

Expected values: 5 - 110 ml/cm H2O

Tidal volume (TV/PBW) **-** record the most recent value prior to ventilator discontinuation.

Expected values: 4 - 12 ml/kg

Minute ventilation (MV) - record the most recent value prior to ventilator discontinuation.

Rules:

1. Use the corrected minute ventilation

Expected values: 6 - 20 ml/min

Spontaneous breathing trial (SBT) **-** record if an SBT was done or not (yes/no) within the 24 hours prior to ventilator discontinuation.

> ***Where to look*:** take this information from the 'RESPIRATORY CARE INPATIENT RECORD', looking under ventilator mode for 'SBT.'
>
> **Rules:**
>
> 1. If not documented there, then look under 'SPONT PARM' (spontaneous parameters).
> 2. If no mention of a SBT there, then look at 'VITAL SIGNS FLOW SHEET' under 'INPT - FLOWSHEETS AND MAR' for documentation on an SBT.

Misc

Glasgow coma scale - record the lowest GCS prior to ventilator discontinuation.

> ***Where to look:*** look at GCS total score under 'ASSESSMENT FLOWSHEET' under 'INPT - FLOWSHEETS AND MAR'.
>
> **Rules:**
>
> 1. If not documented there then look under Vital signs, CIS notes, or inpatient progress notes to identify the lowest GCS documented prior to ventilator discontinuation.
>
> Expected values: 2 - 15

Hemodynamics

Where to look: take this information from the 'VITAL SIGNS FLOW SHEET' under 'INPT - FLOWSHEETS AND MAR'.

Mean arterial pressure (MAP) - record the lowest sustained MAP, defined as the two lowest MAP values that are documented for > 30 minutes during the 24 hours prior to ventilator discontinuation.

> ***Where to look****:* take this information from the 'VITAL SIGNS FLOWSHEET' under 'INPT - FLOWSHEETS AND MAR'.
>
> **Rules:**
>
> 1. Use the mean arterial pressure (MAP) of the noninvasive blood pressure reading.
> 2. Find the two lowest (MAP) values with the lowest mean MAP that occur during the 24 hour period prior to ventilator discontinuation. Record values that are documented for more than 30 minutes, but are ≤ 90 minutes apart.
>
>   Example (values that would be recorded are highlighted):
>
> | Time | 1200 | 1245 | 1255 | 1300 | 1400 |
> |---|---|---|---|---|---|
> | MAP | 75 | 78 | 76 | 76 | 77 |
>
> The values at 1245 and 1255 were not sustained for > 30 minutes and are thus not recorded. The values at 1200 and 1300 generate the lowest mean MAP and are greater than 30 minutes, but less than 90 minutes apart.

IABP (Intraaortic balloon pump) - record the presence or absence (yes/no) of a balloon pump.

> ***Where to look****:* take this from the 'VITAL SIGNS FLOWSHEET'. It may also be documented under the 'IABP' or 'IV lines' section.

Medications

Rules:

1. Round cumulative drip rates to the nearest 15 minute interval.

   Round down to 0 if < 7 min
   Round to 15 minutes if ≥ 8 but < 23 min
   Round to 30 minutes if ≥ 23 but < 38 min
   Round to 45 minutes if ≥ 38 minutes but < 53 min
   Round to 1 hour if ≥ 53 min

Neuromuscular blocking agent - record the presence (yes/no) of a continuous infusion neuromuscular blocking agent prior to ventilator discontinuation.

> ***Where to look:*** take this from the 'DRIPS' section under 'VITAL SIGNS FLOWSHEET' under 'INPT - FLOWSHEETS AND MAR'.
>
> Common neuromuscular blocking agent names:
>
> Atracurium
> Cisatracurium
> Doxacurium
> Metocurine
> Mivacurium
> Pancuronium
> Pipecuronium
> Rocuronium
> Succinylcholine
> Tubocurarine
> Vecuronium

Vasopressors - record the highest dose rate documented on 2 recordings at least 30 minutes apart within the 24 hours prior to ventilator discontinuation. Record the drip rate at <u>one hour</u> prior to ventilator discontinuation.

> ***Where to look****:* take this from the 'DRIPS' section under 'VITAL SIGNS FLOWSHEET' under 'INPT - FLOWSHEETS AND MAR'.
>
> **Rules:**
>
> 1. Record the bottom number listed in the box.
>
>   Ex: Dopamine 5.0/4.0, then record 4.0
>
> Common vasopressor names:
>
> Dobutamine
> Dopamine
> Norepinephrine
> Epinephrine
> Phenylephrine

Sedation/analgesia - record the dose rate at the time of ventilator discontinuation and record the cumulative dose in the 24 hours prior to ventilator discontinuation.

Where to look: take the drip rates from the 'VITAL SIGNS FLOWSHEET' under 'INPT - FLOWSHEETS AND MAR'. Take the PRN doses from the 'MEDICATION ADMINISTRATION RECORD'. These may be listed under RTN, Once, or PRN.

Rules:

1. **I**f more than one drip rate is listed use the BOTTOM number

   Ex. Propofol 5/8.2, use 8.2
   Lorazepam 4/4, use 4

2. For the cumulative dose in the 24 hours prior to ventilator discontinuation you need to add up the total from the drip THEN look for PRN doses. Calculate the cumulative drip dose using the drip rate recorded for each time period.

   Ex: If a drip rate of 2 mg/hr is recorded at 1200 and 1300, then changed to 4 mg/hr at 1400, use the rate of 2 mg/hr for 2 hours (i.e. from 1200-1400), then begin using the new dose for the time period which follows the dose change to 4 mg/hr.

   Drip: 1 mg/hr x 8 hours + 2mg/hr x16 hours = 40 mg

   PRN: 4mg bolus x 2 = 8mg

   Total cumulative = Drip + PRN = 40 + 8 = 48 mg

3. If Propofol PRN doses are given, then need to record patient's weight.

Common opioid analgesic names:	Fentanyl Morphine Hydromorphone Oxycodone Methadone Oxymorphone Levorphanol
Common benzodiazepine names:	Alprazolam Chlordiazepoxide hydrochloride Clonazepam Clorazepate dipotassium Diazepam Halazepam Lorazepam Oxazepam Prazepam Flurazepam hydrochloride Quazepam Temazepam Triazolam
Other common sedatives:	Propofol Phenobarbital

Appendix B

Summary of Abstract Doubling Results

21 charts were doubled, representing approximately 6% of the charts.

There are 114 data elements on the form.

Chart	Percent agreement
1	98.25
2	99
3	98.25
4	100
5	98.25
6	100
7	100
8	100
9	99
10	99
11	91
12	99
13	98
14	100
15	99
16	99
17	99
18	96
19	99
20	99
21	97