Time to Death after Terminal Withdrawal of Mechanical Ventilation: Specific Respiratory and Physiologic Parameters May Inform Physician Predictions

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Abstract

Background: 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.

Objectives: The study objective was to aid physician communication about the dying process by identifying predictors of time to death after terminal withdrawal of mechanical ventilation.

Methods: We conducted an observational analysis from a single-center, before–after evaluation of an intervention to improve palliative care. We studied 330 patients who died after terminal withdrawal of mechanical ventilation. Predictors included patient demographics, laboratory, respiratory, and physiologic variables, and medication use.

Results: The median time to death for the entire cohort was 0.58 hours (interquartile range (IQR) 0.22–2.25 hours) after withdrawal of mechanical ventilation. Using Cox regression, independent predictors of shorter time to death included higher positive end-expiratory pressure (per 1 cm H₂O hazard ratio [HR], 1.07; 95% CI 1.04–1.11); higher static pressure (per 1 cm H₂O HR, 1.03; 95% CI 1.01–1.04); extubation prior to death (HR, 1.41; 95% CI 1.06–1.86); and presence of diabetes (HR, 1.75; 95% CI 1.25–2.44). Higher noninvasive mean arterial pressure predicted longer time to death (per 1 mmHg HR, 0.98; 95% CI 0.97–0.99).

Conclusions: Comorbid illness and key respiratory and physiologic parameters may inform physician predictions of time to death after withdrawal of mechanical ventilation. An understanding of the predictors of time to death may facilitate discussions with family members of dying patients and improve communication about end-of-life care.

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} Studies evaluating time to death after terminal withdrawal of life-sustaining measures in adults suggest that 45% to 76% of

deaths occur within 60 minutes,^{6–13} and the majority of patients die within 24 hours.¹⁴ Although physicians are encouraged to address expected time to death after withdrawal of life-sustaining measures, residual uncertainty in predicting time to death may discourage routine discussion of this important issue. The majority of studies evaluating time to death after withdrawal of life-sustaining measures have assessed time to death as a dichotomous outcome (death within 60 minutes versus death occurring after this time).^{6–12,15,16} Utilization of time to death in a continuous fashion may better identify independent predictors of time to

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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,¹⁷ 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. We also evaluated associations between 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 time to death, but that sedatives or analgesics provided prior to withdrawal would not.

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 care to critically ill patients and their family members.¹⁷ Eligible patients were those who died after a minimum ICU stay of six hours before death or within 30 hours after being transferred to another hospital location from the ICU. Patients were identified by examining hospital admission, discharge, and/or transfer records daily during two time periods: before (July 2003 to March 2004) and after (December 2004 to October 2005) the intervention. Eligible patients were enrolled consecutively. The study included 590 patients (preintervention, $n = 253$; postintervention, $n = 337$) receiving care in a university-based, inner city level I trauma center with medical, surgical, cardiac, and neurocritical care units. 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 included patients underwent terminal withdrawal of mechanical ventilation ($n = 330$). The University of Washington Human Subjects Division approved all study procedures.

Data collection and variables

Retrospective medical record review was completed in two phases. Initial abstraction was completed during the before–after study by trained chart abstractors using a standardized chart abstraction protocol. During the second abstraction period the study's researchers collected additional clinical and physiological variables using similar chart abstraction protocols, training, and reliability reviews. Co-review of randomly selected charts (6% sample) resulted in >90% agreement on all items.

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 epi-

sode of withdrawal of ventilator support most proximal to death. Eight patients died during the process of withdrawal 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. Patient-level characteristics included patient age (in years), gender (male/female), race/ethnicity (non-Hispanic white/other), insurance status (private/Veterans Affairs/Medicare or under/uninsured), and medical comorbidities. Comorbidities were based on identification of the condition in the

TABLE 1. PATIENT CHARACTERISTICS AND HOSPITALIZATION INFORMATION

	N = 330
Age, mean years (SD)	61 (17)
Sex, n (%)	
Female	119 (36)
Male	211 (64)
Race, n (%)	
White, non-Hispanic	262 (79)
Other race/ethnicity	52 (16)
Missing	16 (5)
Insurance type, n (%)	
Private, VA, or Medicare	239 (72)
Under- or uninsured	91 (28)
Comorbidities, n (%)	
Diabetes	64 (19)
Chronic respiratory disease	58 (18)
Congestive heart failure	40 (12)
Malignancy	40 (12)
Cerebrovascular disease	34 (10)
Hospital admission source, n (%)	
Home	147 (45)
Acute care facility	141 (43)
Skilled nursing facility	18 (5)
Homeless	9 (3)
Group home	7 (2)
Office/clinic	4 (1)
Rehab	2 (1)
Missing	2 (1)
ICU admission source, n (%)	
Emergency department	247 (75)
Hospital floor/observation unit	54 (16)
Operating room/procedure recovery	26 (8)
Direct admission	3 (1)
ICU discharge service, n (%)	
Neurosurgery	90 (27)
Medicine	77 (23)
General surgery	57 (17)
Neurology	49 (15)
Intensivist or pulmonary/critical care	40 (12)
Surgical subspecialty	12 (4)
Cardiology	4 (1)
Cardiothoracic surgery	1 (0.3)
ICU LOS prior to withdrawal, mean days (SD)	7 (8)

ICU, intensive care unit; LOS, length of stay.

medical record and include diabetes, chronic respiratory disease, congestive heart failure, malignancy, or cerebrovascular disease. Laboratory values 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 (10⁹/L). 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), and minute ventilation (L/min).

We also noted performance of a spontaneous breathing trial within the 24 hours prior to withdrawal. For neurologic status, we abstracted the lowest Glasgow Coma Scale (GCS) score (range 2–15)¹⁸ within the 24 hours prior to withdrawal. For hemodynamic status, we recorded the two lowest mean arterial pressure (MAP mmHg) values that were documented for

>30 minutes during the 24 hours prior to ventilator discontinuation, then averaged those values for a final estimate. Documentation of extubation prior to death and presence or absence of an intra-aortic balloon pump (IABP) in the 24 hours prior to withdrawal were also recorded. We included medications that might be associated with time to death after withdrawal of mechanical ventilation, including vasoactive agents, sedatives, and analgesics. Vasopressors or inotropes (norepinephrine, dopamine, dobutamine, epinephrine, vasopressin, and phenylephrine) were categorized according to the number of agents a patient received in the hour prior to ventilator withdrawal. Total doses of sedatives and/or analgesics (opiates, benzodiazepines, and propofol) in the 24 hours prior to withdrawal were also recorded. Total opioid dose included the following medications, expressed as morphine equivalents: morphine, fentanyl, hydromorphone, oxycodone, and meperidine. Total benzodiazepine dose included the following medications, expressed as lorazepam equivalents: lorazepam, midazolam, and diazepam.

TABLE 2. CLINICAL VARIABLES AND MEDICATION USE IN THE 24 HOURS PRIOR TO WITHDRAWAL OF MECHANICAL VENTILATION

	Total N = 330		
	n	Missing, n (%)	% or mean (SD)
Laboratory variables			
pH, mean (SD)	304	26 (8)	7.39 (0.11)
Arterial PaO ₂ (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)	1.68 (1.50)
Platelets (10 ⁹ /L), mean (SD)	306	24 (7)	190 (118)
Respiratory variables			
FiO ₂ (% from ventilator), mean (SD)	322	8 (2)	54 (24)
PEEP (cm H ₂ O), mean (SD)	318	12 (4)	7 (4)
Static pressure (cm H ₂ O), mean (SD)	297	33 (10)	26 (9)
Minute ventilation (L/min), mean (SD)	312	18 (5)	11 (4)
Spontaneous breathing trial, %		8 (2)	
No	278	-	84
Yes	44	-	13
Extubated prior to death, %		4 (1)	
No	83	-	25
Yes	243	-	74
Physiologic variables			
GCS (2–15), mean (SD)	321	9 (3)	4 (2)
Noninvasive MAP (mmHg), mean (SD)	321	9 (3)	73 (15)
Presence of IABP, %		17 (5)	
No	310	-	94
Yes	3	-	1
Medications prior to withdrawal			
Vasopressors/inotropes in the hour prior to withdrawal, %		2 (1)	
None	248	-	75
One	55	-	17
More than one	25	-	8
Total dose of opioids previous 24 hrs (mg), ^a mean (SD)	328	2 (1)	94 (264)
Total dose of benzodiazepines previous 24 hrs (mg), ^b mean (SD)	328	2 (1)	17 (42)
Total dose of propofol previous 24 hrs (mg), mean (SD)	328	2 (1)	414 (1236)

FiO₂, fraction of inspired oxygen; GCS, Glasgow Coma Scale; IABP, intra-aortic balloon pump; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen; PEEP, positive end-expiratory pressure.

^aTotal opioid dose includes the following medications expressed as morphine equivalents: morphine, fentanyl, hydromorphone, oxycodone, and meperidine.

^bTotal benzodiazepine dose includes the following medication expressed as lorazepam equivalents: lorazepam, midazolam, and diazepam.

Data analysis

We used Kaplan-Meier survival plots to describe time to death. 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 identify independent predictors of time to death. An HR >1.0 represents a covariate associated with a shorter time to death (i.e., an increased risk of death) whereas a HR <1.0 suggests a longer time to death (i.e., decreased risk of death). For categorical data, missingness was addressed by including a category to represent missing cases. No variable included in our analysis had >10% missing data.

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. Selected covariates were included in a final multivariable model that retained patient age, race/ethnicity, sex, and insurance status. Covariates in the final model did not demonstrate evidence of violation of the proportional hazards assumption. Analyses were performed using Stata statistical software version 13.0 (StataCorp, College Station, TX) with statistical significance for all hypothesis tests set at $P < 0.05$.

Results

Baseline characteristics of the cohort are described 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 were insured through private insurance, Veterans Affairs, 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 were admitted to the ICU from the emergency department (75%). The most common ICU discharge services were Neurosurgery, Medicine, and General Surgery. Average length of stay in the ICU prior to withdrawal was seven days (SD 8). Clinical variables and medication utilization in the 24 hours prior to withdrawal of mechanical ventilation 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 (see Fig. 1). Median time to death for those surviving more than one hour ($n=133$) was three hours.

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

Men had shorter times to death than women. 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 (see Table 3).

Clinical predictors of time to death after withdrawal adjusted for patient demographics

Higher pH, bicarbonate level, and platelet count were all associated with a longer time to death. Higher creatinine was

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

TABLE 3. UNADJUSTED ASSOCIATIONS BETWEEN TIME TO DEATH AFTER WITHDRAWAL OF MECHANICAL VENTILATION AND PATIENT DEMOGRAPHICS AND COMORBIDITIES^a

	n	<i>Time to death, hours</i>		<i>P value</i>
		<i>Median</i>	<i>IQR</i>	
Age, years				0.051
≤50	81	0.48	0.17–2.30	
51–60	70	1.28	0.33–4.90	
61–70	56	0.57	0.22–2.70	
71–80	79	0.50	0.17–1.50	
>80	44	0.47	0.24–1.40	
Sex				0.001
Female	119	0.83	0.37–3.10	
Male	211	0.42	0.17–2.00	
Race/ethnicity				0.250
White, non-Hispanic	262	0.67	0.20–2.30	
Other	52	0.38	0.22–1.70	
Insurance type				0.330
Private, VA, or Medicare	239	0.53	0.18–2.30	
Under- or uninsured	91	0.67	0.27–2.40	
Diabetes				0.035
No	266	0.68	0.22–2.60	
Yes	64	0.47	0.18–1.00	
Chronic respiratory disease				0.480
No	272	0.52	0.20–2.30	
Yes	58	0.74	0.25–2.20	
Congestive heart failure				0.550
No	290	0.58	0.22–2.40	
Yes	40	0.63	0.23–1.20	
Malignancy				0.960
No	290	0.55	0.22–2.30	
Yes	40	0.68	0.23–2.00	
Cerebrovascular disease				0.045
No	296	0.51	0.20–2.10	
Yes	34	1.43	0.50–2.50	

IQR, interquartile range.

^aTime to death after withdrawal was not a normally distributed variable. Thus nonparametric Wilcoxon rank-sum test or Kruskal-Wallis equality-of-populations rank test were used.

associated with a shorter time to death. Among the respiratory variables, higher FiO₂, PEEP, static pressure, and minute ventilation were associated with shorter time to death. A spontaneous breathing trial in the 24 hours prior to withdrawal was associated with longer time to death. Patients with higher GCS scores or higher noninvasive mean arterial pressure were more likely to live longer after withdrawal. The presence of an IABP prior to withdrawal was associated with a shorter time to death. Those receiving more than one vasopressor or inotrope in the hour prior to withdrawal also had shorter times to death. Higher total dose of opioids and total dose of benzodiazepines were both associated with a shorter time to death (see Table 4).

Multivariable model of time to death after withdrawal

Results from a final multivariable model are provided in Table 5. Diabetes was a predictor of shorter time to death. Extubation, higher PEEP, and higher static pressure were associated with shorter time to death. Higher noninvasive MAP was associated with a longer time to death. Total doses of sedatives or analgesics provided in the 24 hours prior to death were not predictors of 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 withdrawal of life-sustaining measures have utilized a dichotomous outcome, comparing death within 60 minutes to death occurring after this time.^{6–12,15,16} The use of Cox regression, as compared to creation of a binary outcome and use of logistic regression, avoids creation of an arbitrary cut-point and allows more effective use of patient data. With this approach we were able to identify several independent predictors of time to death. Our study has several additional strengths, including a large sample size and diverse ICU population. Most studies of time to death after withdrawal of life-sustaining measures include fewer than 230 patients^{7–11,15,19} and many occur in the neurocritical care setting.^{8–10} Our study sample included 330 patients drawn from a variety of medical and surgical ICUs. Finally, we utilized a unique variety of laboratory and respiratory variables, including bicarbonate, creatinine, and platelet count as well as performance of a spontaneous breathing trial and extubation prior 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 predictors of shorter time to death.^{7,12,13,16,19} 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 makes sense from a physiologic perspective, given the likelihood for rapid deterioration in both oxygenation and ventilation in patients requiring more support from mechanical ventilation.

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.^{20,21} Blood pressure parameters have also been associated with time to death,

TABLE 4. PREDICTORS OF TIME TO DEATH AFTER TERMINAL WITHDRAWAL OF MECHANICAL VENTILATION, ADJUSTED FOR DEMOGRAPHIC VARIABLES^a

	n ^b	Unadjusted			Adjusted for age, sex, race, insurance		
		HR	95% CI	P value	HR	95% CI	P value
Laboratory variables							
pH	304	0.07	0.02–0.20	<0.001	0.06	0.02–0.20	<0.001
Arterial PaO ₂ (mmHg)	304	1.00	1.00–1.00	0.180	1.00	1.00–1.00	0.190
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	0.032
Platelets (10 ⁹ /L)	306	1.00	1.00–1.00	0.001	1.00	1.00–1.00	0.001
Respiratory variables							
FiO ₂ (% from ventilator)	322	1.01	1.01–1.02	<0.001	1.02	1.01–1.02	<0.001
PEEP (cm H ₂ O)	318	1.10	1.07–1.13	<0.001	1.10	1.07–1.13	<0.001
Static pressure (cm H ₂ O)	297	1.04	1.02–1.05	<0.001	1.04	1.03–1.05	<0.001
Minute ventilation (L/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	0.046
Extubated prior to death							
No	83	1.00	Referent		1.00	Referent	
Yes	243	1.13	0.88–1.46	0.328	1.15	0.89–1.49	0.296
Physiologic variables							
GCS (2–15)	321	0.94	0.89–1.00	0.054	0.94	0.88–0.99	0.026
Noninvasive MAP (mmHg)	321	0.98	0.97–0.99	<0.001	0.98	0.97–0.99	<0.001
Presence of IABP							
No	310	1.00	Referent		1.00	Referent	
Yes	3	2.74	0.88–8.58	0.083	4.12	1.17–14.50	0.027
Medications prior to withdrawal							
Vasopressors/inotropes one hr prior							
None	211	1.00	Referent		1.00	Referent	
One	81	1.60	1.19–2.15	0.002	1.54	1.15–2.08	0.004
More than one	36	3.38	2.20–5.17	<0.001	3.21	2.06–4.95	<0.001
Total opioid dose 24 hrs prior	328	1.00	1.00–1.00	0.124	1.00	1.00–1.00	0.043
Total benzodiazepine dose 24 hrs prior	328	1.00	1.00–1.01	0.039	1.00	1.00–1.01	0.018
Total propofol dose 24 hrs prior	328	1.00	1.00–1.00	0.345	1.00	1.00–1.00	0.357

FiO₂, fraction of inspired oxygen; GCS, Glasgow Coma Scale; HR, hazard ratio; IABP, intra-aortic balloon pump; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen; PEEP, positive end-expiratory pressure.

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

^bFor categorical variables, missing data were included as a separate category, not shown here.

with higher systolic blood pressure identified as a predictor of longer time to death.^{7,12} In our study, higher noninvasive MAP was similarly associated with longer time to death. This is biologically plausible, as a lower MAP may reflect greater severity of illness and would leave the patient with less hemodynamic reserve upon initiation of the withdrawal process.

Extubation prior to death has been included in prediction tools used to identify candidates for donation after circulatory death,¹⁵ given the potential connection between loss of airway protection and shorter time to death. Few studies, however, have utilized multivariable analysis to assess extubation as a predictor of time to death. In the two studies in which extubation was assessed, neither detected an association between extubation and time to death within 60 minutes of withdrawal.^{6,11} Our analysis assessed time to death as a continuous outcome and identified a higher risk of death among patients who underwent extubation. Given the role an endotracheal tube plays in maintaining airway protection, it is feasible that intubated patients may be able to maintain oxygenation and ventilation after withdrawal of mechanical

ventilation more readily than those who undergo extubation. Decisions about extubation after a decision to forgo life-sustaining treatments should incorporate the desires of surrogate decision makers and also consider patient comfort. In one study examining duration of life support withdrawal and its association with overall family satisfaction with care in the ICU, extubation was associated with higher family satisfaction with care.²² The presence of an endotracheal tube may prolong the dying process and may interfere with patient-family interactions.

The association between shorter time to death and a history of diabetes is interesting, and there are several potential explanations for this association. 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.²³ 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

TABLE 5. MULTIVARIABLE MODEL OF PREDICTORS OF TIME TO DEATH AFTER TERMINAL WITHDRAWAL OF MECHANICAL VENTILATION^a

	n ^b	HR	95% CI	P value
Age, years	330	1.01	1.00–1.02	0.187
Sex				
Female	119	Referent		
Male	211	1.27	0.98–1.66	0.073
Race				
White, non-Hispanic	262	Referent		
Other	52	1.13	0.80–1.61	0.488
Insurance type				
Under- or uninsured	91	Referent		
Private, VA, or Medicare	239	1.02	0.74–1.40	0.908
Diabetes				
No	266	Referent		
Yes	64	1.75	1.25–2.45	0.001
Cerebrovascular disease				
No	296	Referent		
Yes	34	0.70	0.45–1.08	0.108
pH	304	0.37	0.09–1.59	0.181
PEEP (cm H ₂ O)	318	1.07	1.04–1.11	<0.001
Static pressure (cm H ₂ O)	297	1.03	1.01–1.04	0.006
Extubated prior to death				
No	83	Referent		
Yes	243	1.41	1.06–1.86	0.017
Noninvasive MAP (mmHg)	321	0.98	0.97–0.99	0.004
Presence of IABP				
No	310	Referent		
Yes	3	2.64	0.75–9.30	0.130
Total opioid dose 24 hours prior	328	1.00	1.00–1.00	0.064
Total benzodiazepine dose 24 hours prior	328	1.00	1.00–1.01	0.450

FiO₂, fraction of inspired oxygen; GCS, Glasgow Coma Scale; HR, hazard ratio; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure.

^aEstimates from multivariable Cox proportional hazards regression. Variables selected for this model via backward stepwise regression with $P=0.2$. Variables removed from this model included chronic respiratory disease, congestive heart failure, malignancy, arterial PaO₂, bicarbonate, creatinine, platelets, FiO₂, minute ventilation, spontaneous breathing trial, GCS, vasopressors/inotropes, and total dose of propofol.

^bFor categorical variables, missing data for each variable were included in the final model as separate categories, not shown here. Final model $n=275$.

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.

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 well studied previously. Second, there was missing data for several of our predictors of interest. Though missingness was addressed for categorical variables by including a category to represent missing cases, missing data for continuous variables may lead to biased estimates. No variable included in our analysis had >10% missing data. Importantly, patients who were in the ICU for

less than 6 hours or who died more than 30 hours after transfer out of the ICU were excluded. This limits our ability to extrapolate our findings to those who die within the first hours of ICU admission or those who die after days spent on the acute care floor. Finally, it is important to note that our goal was not to provide physicians with a precise clinical prediction rule, per se, but to identify predictors which, when present, could allow physicians to provide some guidance when a family specifically requests information about time to death after withdrawal. It is also important to note that such guidance should always include an expression of the uncertainty involved in predicting the future.

For family members of dying patients, it is essential that physicians provide 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. In addition, 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. It is important that we acknowledge the uncertainty that exists

in predictions of time to death when talking with family members, but at the same time we should use the data presented here and in other studies to enhance conversations about end-of-life care with family members of critically ill patients. Most patients undergoing withdrawal of life-sustaining therapies will die within several hours of withdrawal, and the vast majority within 24 hours. Numerous studies, including this one, have identified respiratory parameters and hemodynamic status as important predictors of time to death. By understanding the typical trajectory of dying for these patients and integrating these predictors into discussions 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.

Author Disclosure Statement

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