Safety of Extubating Mechanically Ventilated Patients on Vasoactive Infusions: A Retrospective Cohort Study

Tara Quasim, Martin Shaw, Joanne McPeake, Martin Hughes, Theodore J Iwashyna *

Tara Quasim MD, MPH, MBChB
University of Glasgow, School of Medicine, Dentistry and Nursing, Scotland, UK
NHS Greater Glasgow and Clyde, Glasgow Royal Infirmary, Intensive Care Unit, Scotland, UK

Martin Shaw, PhD
NHS Greater Glasgow and Clyde, Glasgow Royal Infirmary, Clinical Physics Department, Scotland, UK

Joanne McPeake PhD, MSc, BN (Hons)
University of Glasgow, School of Medicine, Dentistry and Nursing, Scotland, UK
NHS Greater Glasgow and Clyde, Glasgow Royal Infirmary, Intensive Care Unit, Scotland, UK

Martin Hughes, MBChB, BSc
NHS Greater Glasgow and Clyde, Glasgow Royal Infirmary, Intensive Care Unit, Scotland, UK

Theodore J Iwashyna, MD, PhD * corresponding author
Center for Clinical Management Research, VA Ann Arbor Health System, Ann Arbor, Michigan, USA
Department of Internal Medicine, Division of Pulmonary and Critical Care, University of Michigan
2800 Plymouth Road
NCRC Building 16, Room 326W
Ann Arbor, Michigan, USA
tiwashyn@umich.edu twitter: @iwashyna

Acknowledgements: JMcP is supported by a CNO Scotland Fellowship and the Health Foundation. TJI work was supported, in part, by US Department of Veterans Affairs, Health Services Research & Development, IIR 13-079.
JMcP and TQ are supported by the Health Foundation.

Contributions: Conception and design: all; Data Extraction and Primary Analysis: MS, JMcP; Analysis and interpretation: all; Drafting and revising the manuscript for important intellectual content: all

Disclaimer: This does not necessarily represent the official views of the US Government or Department of Veterans Affairs.

Word Count: 933 excluding references

Discontinuation of vasopressors or inotropes is a common pre-condition for spontaneous breathing trials or extubation in U.S. clinical trials and guidelines.[1-4] A contrary view is that such a delay increases patients' risks for the complications of endotracheal intubation and mechanical ventilation[5] and may mandate additional intensive care unit (ICU) time, decreasing throughput and effective ICU capacity.[6]

Glasgow Royal Infirmary ICU (GRI) extubates select patients whilst on vasopressors/inotropes ('vasoactive infusions'), but the safety of this procedure has never been formally evaluated. We asked: "Among intubated patients who ever receive vasoactive infusions, are extubations attempted whilst patients are still on vasoactive infusions associated with different ICU mortality (primary outcome) than extubations attempted after the infusions have been stopped?" Secondary outcomes included reintubation, hospital mortality, and ICU and hospital lengths of stay.

GRI is a 20 bed mixed medical/surgical ICU with tertiary referrals for burn, upper gastrointestinal, and pancreatic care. It does not have cardiothoracic services on site and does not routinely admit elective surgical patients with an uneventful intraoperative course. Neither an extubation protocol nor formal SBTs are routinely employed. Clinical practice is to extubate patients—at the attending physician's discretion—who have minimal ventilatory and oxygen support, an adequate cough, and ideally are able to participate with physiotherapy.

This retrospective study included all patients intubated from January 2007 to February 2017, who received a vasoactive infusion while intubated. Each patient's first extubation attempt was analyzed, as patients who have previously failed an extubation are managed in different ways. We did not include readmissions in the same hospital

episode and the ICU death was defined as death arising from the index ICU admission. Patients receiving 0 to 0.1 mg/hr of noradrenaline, adrenaline, metaraminol, or dobutamine at the time of their extubation were excluded (n=43) as this is a marginal dose. Also excluded were those who: died prior to a first extubation attempt; self-extubated (n=4); and were extubated explicitly onto a palliative care pathway (n=6). De-identified data were extracted from operational electronic data systems. Data were analyzed in R (R Core Team 2017, Version 3.4.3). Continuous variables were analyzed using the Mann-Whitney U tests, categorical variables were compared using chi-square tests, analyses at risk of censoring (e.g., reintubation rates) due to ICU mortality were performed with censored time to event analysis, and multivariable logistic regression used for adjustment for ICU admission characteristics.[7]

Ethics approval was formally deemed unnecessary for these de-identified data.

There were 4008 intubated ICU patients in the study period, of whom 1319 met inclusion criteria; 43 were excluded as they were extubated on marginal doses of vasoactive agents, 4 because they self-extubated, and 6 because they were extubated directly for palliative care. The primary study cohort thus consisted of 1266 patients: 280 patients (21%) extubated on vasoactive infusions and 986 extubated after discontinuation. Patients extubated on vasoactive medications were somewhat less ill at presentation (APACHE II 19 vs. 21, p=0.007).

There was no difference in ICU mortality between the two groups (n=18 deaths (6.4%) on vasoactive medications vs. n=80 (8.1%) off, p=0.42). There was no difference in the in-ICU re-intubation rate between the 2 groups (n=30 reintubations (10.7%) on vasoactive infusions vs. n=120 (12.2%), p=0.58. Patients extubated on vasoactive

infusions had a slightly shorter ICU stay after extubation (2 days vs. 2.2 days, p=0.049), but a shorter overall ICU LOS (5 days vs. 9 days, p<0.001) and duration of mechanical ventilation (2 days vs. 6 days, p<0.001). **(Table 1).**

In-hospital mortality after first extubation through day 90 is shown in **Figure 1.** There was no statistically significant difference in-hospital mortality in the patients extubated on, as opposed to off vasoactive medications (total in-hospital mortality: n=51 (18.2%) vs n=137 (13.9%), p=0.09), with a median time from extubation to death of 9.6 days (2.4-22.4 days); this was longer among decedents extubated on vasoactive medications (15.5 days (7.5, 31) vs 9.5 days (1.2, 18.5), p=0.005).

After multivariable adjustment for differences between the groups at ICU admission—include age, APACHE II, dialysis during ICU stay, and ICU diagnosis — there is no significance difference for any of the outcomes between those extubated on vasoactive agents and those extubated not on vasoactive agents (hospital mortality adjusted p value = 0.0805, unit mortality adjusted p-value = 0.332 and reintubation adjusted p-value = 0.8383).

In summary, in this large single center study, 21% of intubated patients who received infusions of vasoactive infusions while mechanically ventilated were extubated for the first time whilst still receiving them. Coincident with their earlier extubation, their ICU length of stay was shorter without an increase in ICU mortality, hospital mortality or reintubation rate, suggesting that this can be safe practice. Rates of reintubation were similar to published U.S. rates among comparable emergent surgical (10.7%), medical (10.7%), and trauma (13.5%) patients.[8]

These single center data suggest that current U.S. clinical trial practice and guidelines may be unnecessarily conservative. In the modern era of lung protective ventilation and reduced sedation, patients may be otherwise ready to extubate prior to full return of hemodynamic stability. Contrary to current practice in recent and ongoing U.S. clinical trials, these data suggest it may be safe to do so in select situations. There are few data on how widespread this practice is.

Limitations of this single center observational data include the absence of random assignment to extubation protocol and the absence of detailed physiologic information matched on day of possible extubation.

These data do not prove that extubation on vasoactive agents is always as safe as other extubations. Instead, they call for the development of protocols for identifying patients who can be safely extubated despite continued vasoactive infusions—thereby speeding ICU recovery—and the rigorous testing of such protocols in randomized evaluations.

Figure 1: Kaplan-Meier Curve showing time to in-hospital mortality, censored at hospital discharge, with 95% confidence intervals.

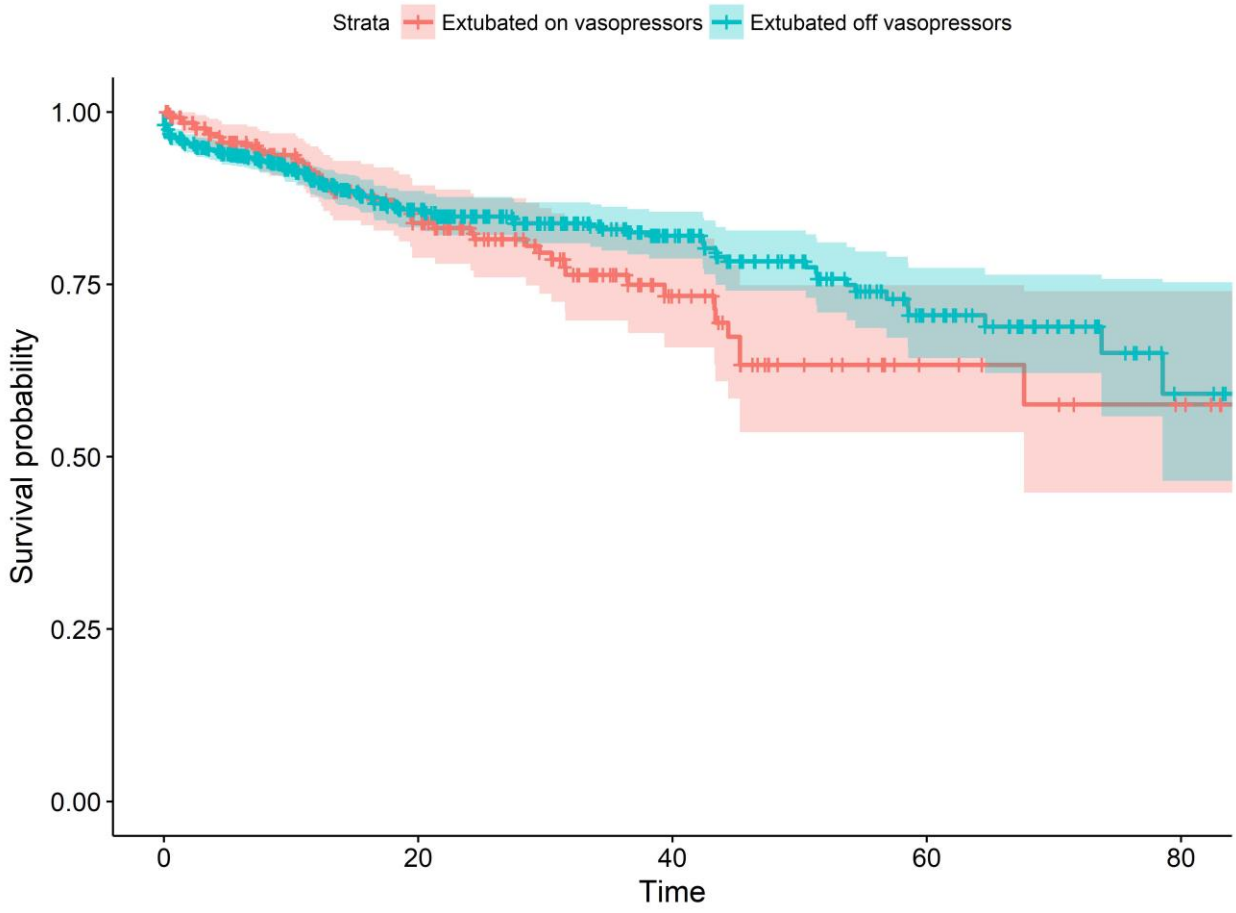

Table 1: Comparison of first time extubation trends within the GRI population. All length of stay variables are calculated in hours and then transformed into days, allowing medians to two significant figures to be calculated. For continuous variables, median plus (interquartile range) is presented.

Variable	Extubated **on** vasopressors (n=280)	Extubated **off** vasopressors (n=986)	p-value
Age	62 (49-73)	59 (47-69)	0.004
Male Gender	148 (52.9%)	568 (57.6%)	0.178
Apache II	19 (14-25)	21 (16-26)	0.007
Renal Replacement	37 (12.4%)	198 (18.9%)	0.011
Specialty			< 0.001
General surgery	149 (53.2%)	374 (37.9%)	
General medicine	61 (21.8%)	362 (36.7%)	
Plastic/Burn surgery	26 (9.3%)	79 (8.0%)	
Other	13 (4.6%)	49 (5%)	
Orthopedic surgery	8 (2.9%)	45 (4.6%)	
Obstetrics	7 (2.5%)	13 (1.3%)	
Urology	7 (2.5%)	17 (1.7%)	
Geriatric medicine	5 (1.8%)	21 (2.1%)	
Gastroenterology	4 (1.4%)	26 (2.6%)	
Comorbidities			0.658
0	1 (0.4%)	9 (0.9%)	
1	218 (77.9%)	758 (76.9%)	
2	47 (16.8%)	156 (15.8%)	
3+	14 (5%)	63 (6.4%)	
Total ICU LOS pre-extubation (days)	0.9 (0.5-1.8)	4.5 (1.8-10)	< 0.001
ICU LOS to first reintubation (days)	0.5 (0.2-1.1)	0.6 (0.2-1.3)	0.699
Total Length of Ventilation (days)	2 (1-4)	6 (3-12)	< 0.001
ICU LOS after extubation until ICU discharge (days)	2 (1-4.6)	2.2 (1.1-5.2)	0.049
Total ICU LOS (days)	5 (3-9)	9 (4-17)	< 0.001
LOS after ICU discharge	14.3 (5.3-30.4)	12.2 (4.3-26.6)	0.032
Time from extubation to death (days)	15.5 (7.5-31.1)	9.5 (1.2-18.5)	0.005
Reintubation Rate	30 (10.7%)	120 (12.2%)	0.575
ICU Mortality on index admission	18 (6.4%)	80 (8.1%)	0.419
Total In-Hospital Mortality	51 (18.2%)	137 (13.9%)	0.09

References

1. MacIntyre NR, Cook DJ, Ely EW, Jr., et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest 2001;120:375S-95S.
2. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 2008;371:126-34.
3. Huang DT, Angus DC, Moss M, et al. Design and Rationale of the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) Trial for Acute Respiratory Distress Syndrome. Ann Am Thorac Soc 2016.
4. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 1996;335:1864-9.
5. Girard TD, Alhazzani W, Kress JP, et al. An Official American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: Liberation from Mechanical Ventilation in Critically Ill Adults. Rehabilitation Protocols, Ventilator Liberation Protocols, and Cuff Leak Tests. Am J Respir Crit Care Med 2016.
6. Terwiesch C, Kc D, Kahn JM. Working with capacity limitations: operations management in critical care. Crit Care 2011;15:308.
7. Hosmer DW, Lemeshow S, May S. Applied Survival Analysis: Regression Modeling of Time to Event Data. New York: Wiley-Interscience; 2008.
8. Miltiades AN, Gershengorn HB, Hua M, Kramer AA, Li G, Wunsch H. Cumulative Probability and Time to Reintubation in U.S. ICUs. Crit Care Med 2017;45:835-42.