Supplementary Online Content

Perkins GD, Mistry D, Gates S; Breathe Collaborators. Effect of protocolized weaning with early extubation to noninvasive ventilation vs invasive weaning on time to liberation from mechanical ventilation among patients with respiratory failure: the Breathe randomized clinical trial. JAMA. doi:10.1001/jama.2018.13763.

This supplementary material has been provided by the authors to give readers additional information about their work.

© 2018 American Medical Association. All rights reserved.

eAppendix. Supplemental Methods

Spontaneous breathing trials
Clinicians were permitted to use one of three types of spontaneous breathing trial in accordance with local unit practices – a T-piece trial, use of CPAP, or low-level pressure support (5-7cm H_2O). A T-piece trial involves the patient breathing spontaneously through their endotracheal tube, with the appropriate inspired oxygen concentration being maintained by a cross-flow device (T-piece). CPAP involved leaving a standing pressure of 5-10 cm H_2O delivered via the ventilator at the top of the endotracheal tube but with no assistance on inspiration. Low-level pressure support trial provided 5-7cm H_2O inspiratory assistance.

The SBT was scheduled to last for at least 30 minutes and could be increased up to 120 minutes in patients considered to be at higher risk of re-intubation (e.g. prolonged ventilation, past history of COPD, heart failure).

During the SBT, patients were closely monitored for signs of distress or fatigue as described by the International Consensus Conference on Weaning [1] A patient was considered to pass the SBT if no signs of distress or fatigue developed. A patient that displayed any sign of distress or fatigue was judged to have failed the SBT. These patients required further weaning and were potentially eligible to be enrolled in the Breathe study.

Physiological assessment:	• Heart rate $\geq$ 20% of baseline or > 140 beats min^{-1}
	• Systolic BP $\geq$ 20% of baseline or > 180mmHg or < 90mmHg
	• Cardiac arrhythmias
	• Respiratory rate $\geq$ 50% of baseline value or > 35 min^{-1}
	• Respiratory rate (min) / tidal volume (L) > 105 min^{-1} l^{-1}
Arterial blood gases:	• PaO_2 < 8 kPa on $FiO_2 \geq 0.5$ or SpO_2 < 90%
	• $PaCO_2$ > 6.5 kPa or increase by > 1 kPa
	• pH < 7.32 or fall by > 0.07 units
Clinical assessment:	• Agitation and anxiety
	• Depressed mental status
	• Sweating / clammy
	• Cyanosis
	• Increased respiratory effort (accessory muscle, facial distress, dyspnoea)

Primary outcome definition and rationale
The primary outcome is time from randomisation to liberation from ventilation.

Liberation from ventilation is defined based on the International Consensus Conference on Weaning recommendations as the time point following which the patient is free of ventilatory (invasive or non-invasive) support for > 48 hours. This defines the duration of weaning process (randomisation to liberation from ventilation). Re-intubation as a consequence of weaning failure occurs within the first 12-48 hours, thus defining weaning success as after 48 hours from liberation of ventilation will capture weaning failures (requiring re-intubation within 48 hours) and exclude events un-related to the weaning process (e.g. the need for an un-related surgical procedure or other event requiring intubation and ventilation).

Explanation for change in sample size
The original sample size was 920 patients to detect a hazard ratio of 0.8 between the intervention and control groups for the primary outcome at 80% power, allowing for attrition due to ICU death and missing outcome data.

After slower than anticipated recruitment, the funder formally reviewed study progress in December 2014. It was noted that the original parameters used for the sample size calculation were not replicated in the trial control arm, specifically that the median duration of ventilation was in fact 2.9 days not 6.4 days as originally anticipated. Based on these data, it was calculated that a sample size of 280 patients would provide 90% power to detect the minimum clinically meaningful median difference of 24 hours between the intervention and control group for the primary outcome at a 5% significance level. This was inflated to 364 to account for attrition and the assumption of non-constant hazards (as quantified by the shape parameter, p, and estimated from the data as 0.918 using the Weibull distribution). The revised sample size was approved following review by the Data Monitoring Committee, Trial Steering Committee and the National Institute for Health Research (NIHR).

Reference

1. 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(25):1864-1869.

© 2018 American Medical Association. All rights reserved.

eTable 1. Type and Outcomes From Spontaneous Breathing Trial

	Invasive weaning (N=182)	Non-invasive weaning (N=182)	Total (N=364)
TYPE OF SBT PERFORMED			
T-PIECE	21 (11.5%)	20 (11.0%)	41 (11.3%)
CPAP	94 (51.6%)	92 (50.5%)	186 (51.1%)
PSUPP	58 (31.9%)	61 (33.5%)	119 (32.7%)
MISSING	9 (5.0%)	9 (5.0%)	18 (4.9%)
DURATION OF SBT (MINUTES)			
MEAN(SD)	46.3 (35.3)	48.5 (37.8)	47.4 (36.5)
MISSING	6	6	12
NUMBER OF CRITERIA FAILED			
1	37 (20.3%)	32 (17.6%)	69 (19.0%)
2	42 (23.1%)	56 (30.8%)	98 (26.9%)
3	49 (26.9%)	48 (26.4%)	97 (26.7%)
4	24 (13.3%)	18 (9.9%)	42 (11.5%)
5	18 (9.9%)	15 (8.2%)	33 (9.1%)
6	6 (3.3%)	8 (4.4%)	14 (3.8%)
7	3 (1.6%)	4 (2.2%)	7 (1.9%)
8	3 (1.6%)	1 (0.5%)	4 (1.1%)
FAILED PHYSIOLOGICAL ASSESSMENTS, N(%)			
HEART RATE > 20% OF BASELINE OR > 140 BEATS MIN^{-1}	56 (30.8%)	34 (18.7%)	90 (24.7%)
SYSTOLIC BP > 20% OF BASELINE OR > 180 MMHG OR < 90MMHG	55 (30.2%)	65 (35.7%)	120 (33.0%)
CARDIAC ARRHYTHMIAS	4 (2.2%)	5 (2.8%)	9 (2.5%)
RESPIRATORY RATE ≥ 50% OF BASELINE VALUE OR > 35 MIN^{-1}	109 (60.0%)	106 (58.2%)	215 (59.1%)
RESPIRATORY RATE MIN-1 / TIDAL VOLUME (L) > 105 MIN^{-1} L^{-1}	30 (16.5%)	23 (12.6%)	53 (14.6%)
FAILED ON ARTERIAL BLOOD GASES, N(%)			
PAO_2 < 8 KPA ON FIO2 > 0.5 OR (SPO2 < 90%)	28 (15.4%)	33 (18.1%)	61 (16.8%)
$PACO_2$ > 6.5 KPA OR INCREASE BY > 1 KPA	24 (13.2%)	22 (12.1%)	46 (12.6%)
PH < 7.32 OR FALL BY > 0.07 UNITS	11 (6.0%)	13 (7.1%)	24 (6.6%)
FAILED CLINICAL ASSESSMENT, N(%)			
AGITATION AND ANXIETY	76 (41.8%)	79 (43.4%)	155 (42.6%)
DEPRESSED MENTAL STATUS	12 (6.6%)	3 (1.7%)	15 (4.1%)
SWEATING / CLAMMY	43 (23.6%)	45 (24.7%)	88 (24.2%)
CYANOSIS	3 (1.7%)	1 (0.6%)	4 (1.1%)
INCREASED RESPIRATORY EFFORT (ACCESSORY MUSCLE, FACIAL DISTRESS, DYSPNOEA)	84 (46.2%)	90 (49.5%)	174 (47.8%)

Note: Patients can have multiple reasons for failing SBT. CPAP (Continous Positive Airway Pressure), Psupp (Pressure support), PaO_2 (arterial oxygen partial pressure), $PaCO_2$ (arterial carbon dioxide partial pressure)

© 2018 American Medical Association. All rights reserved.

eTable 2. Survival Status

Survival	Invasive weaning (N=182)	Non-invasive weaning (N=182)	Adjusted OR (95% CI); p-value	P-value
30 days	157 (86.3%)	158 (86.8%)	0.9 (0.51, 1.73)	0.83
90 days	137 (75.3%)	142 (78.0%)	0.8 (0.49, 1.33)	0.40
180 days	134 (73.1%)	142 (78.0%)	0.7 (0.44, 1.18)	0.19
ICU discharge	157 (86.3%)	160 (87.9%)	0.9 (0.48, 1.70)	0.76
Hospital discharge	146 (80.2%)	147 (80.8%)	0.9 (0.54, 1.58)	0.77

© 2018 American Medical Association. All rights reserved.

eTable 3. Health-Related Quality of Life

			Invasive weaning	Non-invasive weaning	Adjusted estimate (95% CI)*	P-value
EQ-5D Change	Baseline to 3 Months	Mean (SD)	0.13 (0.40)	0.14 (0.42)	0.002 (-0.12, 0.13)	0.98
	Baseline to 6 Months	Mean (SD)	0.04 (0.38)	0.14 (0.40)	0.09 (-0.04, 0.21)	0.16
EQ-5D VAS	3 Months	Mean (SD)	62.5 (20.2)	60.9 (20.0)	-0.6 (-6.71, 5.48)	0.84
	6 Months	Mean (SD)	65.0 (21.2)	61.7 (22.4)	-2.2 (-8.48, 4.04)	0.49
SF-12 (Mental)	3 Months	Mean (SD)	45.8 (10.9)	43.8 (12.6)	-1.5 (-5.14, 2.05)	0.40
	6 Months	Mean (SD)	45.4 (13.3)	44.7 (12.1)	-0.2 (-4.11, 3.77)	0.93
SF-12 (Physical)	3 Months	Mean (SD)	33.7 (9.7)	33.4 (10.3)	-0.4 (-3.69, 2.84)	0.80

© 2018 American Medical Association. All rights reserved.

			Invasive weaning	Non-invasive weaning	Adjusted estimate (95% CI)*	P-value
	6 Months	Mean (SD)	37.0 (10.4)	35.5 (11.6)	-1.8 (-5.36, 1.75)	0.32

** Model adjusted for age, gender, centre, presence/absence of COPD, non-op/op and $PaCO_2$ where centre was included as a random effect. EQ-5D refers to the standardized instrument developed by the EuroQol Group as a measure of health-related quality of life. EQ-5D-3L ranges from -0.59 to 1 with 1 representing perfect health, zero representing death and values below zero suggest health state considered worse than death. EQ-5D VAS (visual analogue scale) ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). SF-12(Short Form-12) physical and mental scores range from 0 to 100 where a higher score indicates better physical/mental functioning.*

© 2018 American Medical Association. All rights reserved.

eTable 4. Subgroup Analyses

Subgroups	Invasive weaning N; median (IQR)	Non-invasive weaning N; median (IQR)	Within group treatment effect (95% CI); P-value*	Interaction effect (95% CI); P-value*
COPD status				
Absence of COPD	150; 108 (57.9, 322.3)	151; 91 (34, 301.7)	HR: 1.1 (0.85, 1.39); 0.517	HR: 1.2 (0.64, 2.15); 0.61
Presence of COPD	32; 128 (38, 442)	31; 107.6 (45.7, 269)	HR: 1.4 (0.78, 2.59); 0.252	
Operative status				
Non-operative	126; 156.2 (58.5, 416)	126; 111.5 (41, 276)	HR: 1.2 (0.94, 1.64); 0.124	HR: 0.7 (0.46, 1.22); 0.24
Post-operative	56; 85.5 (35.4, 255.5)	56; 57 (18.5, 442)	HR: 1.0 (0.63, 1.44); 0.816	
3 main sites vs other				
3 main sites	82; 128 (40, 273)	79; 83 (32, 297)	HR: 1.0 (0.73, 1.44); 0.899	HR: 1.2 (0.76, 1.87); 0.44
Other	100; 108 (59.7, 472.6)	103; 107 (35, 301.7)	HR: 1.2 (0.89, 1.64); 0.218	

* *Model adjusted for age, gender, centre, presence/absence of COPD, non-op/op and post SBT $PaCO_2$ where centre was included as a random effect.*

© 2018 American Medical Association. All rights reserved.