



eAPPENDIX An observational study of end-tidal carbon dioxide trends in general anesthesia

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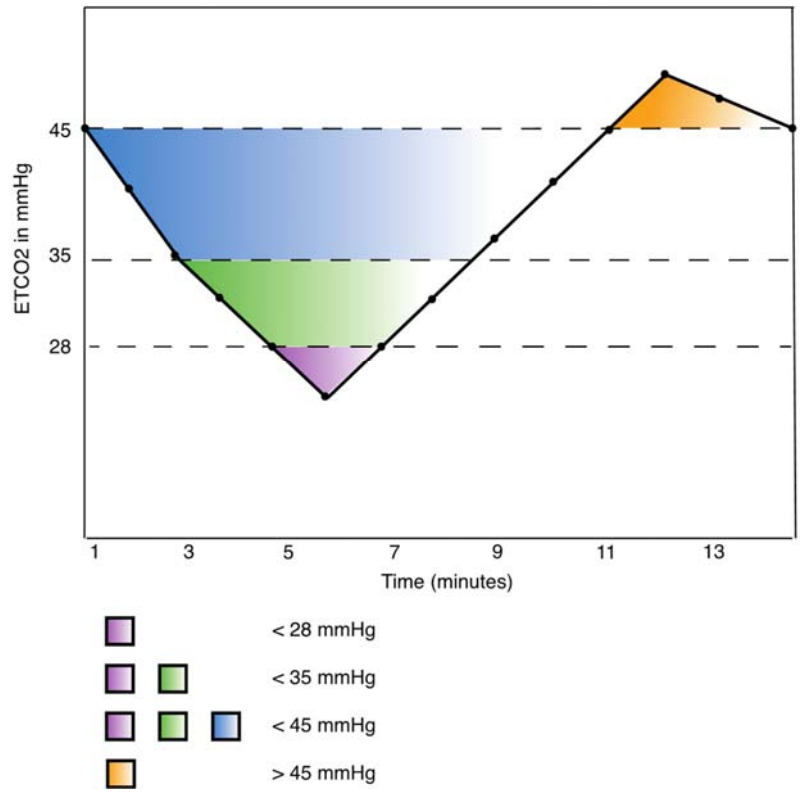
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eTABLE 1 Artifact criteria

Artifact criteria for ventilation parameters and MAP	
General criteria	<ul style="list-style-type: none"> • User entered values: invalid • At least 40 min between incision and the end of the surgical procedure. When incision was not available: at least 50 min between induction end and end of the surgical procedure • At least 20 valid measurements (not consecutive) per case
ETCO₂	<ul style="list-style-type: none"> • ETCO₂ had to be between 10 mmHg (1.3 kPa or 1.3%) and 65 mmHg (8.6 kPa or 8.5%) • Invalid when abrupt changes in ETCO₂ values were seen, defined as ≥ 5 mmHg change in either direction with a consecutive value correcting back with at least 5 mmHg
RMV	<ul style="list-style-type: none"> • Tidal volume had to be between 100 mL and 1000 mL • Respiratory rate had to be between 4 and 25/min • RMV had to be between 500 and 25000 mL·min⁻¹
MAP	<ul style="list-style-type: none"> • Invalid when < 50 mmHg or > 150 mmHg

ETCO₂ = end-tidal carbon dioxide; MAP: mean arterial blood pressure; RMV = respiratory minute volume.

eFIGURE The fitted cubic spline method to calculate the area-under-the-curve for all four ETCO₂ thresholds



ETCO₂ = end-tidal carbon dioxide.

eSURVEY

1. On behalf of which institutions are you completing this survey?

Section 1 Current protocol

2. Is your clinic currently using a protocol entailing an ETCO₂ target or target range?
Example: "40 mmHg according to protocol" or "agreed range of 30–35 mmHg"
3. If yes: please indicate the target that you are using and also provide the unit of measurement (mmHg, kPa, %)
4. If yes: when was this target (approximately) introduced at your institution?
5. If you have any additional comments regarding the current ETCO₂ target, you can leave them here.

Section 2 Past protocol

6. Has your institution used a protocol entailing ETCO₂ targets in the past (between 2008 and 2016) that it is not using anymore?
7. If yes: please indicate the target that you were using and also the unit of measurement (mmHg, kPa, %)
8. If yes: when was this target (approximately) introduced at your institution?
9. If yes: when did your institution (approximately) stop using this target?
10. If you have any additional comments regarding this target, you can leave them here

Section 3 Influencing factors

11. Do you think that, over the years, certain events/policies have influenced the ETCO₂ level at your institution (for example, increased use of spontaneous ventilation mode)?
12. If yes: what was the most important factor that caused a change?
13. If yes: when did this change (approximately) occur?

14. If yes: do you think this change caused the ETCO_2 to increase or decrease?
15. If yes: by approximately how much did this factor increase/decrease the ETCO_2 level?
Please provide the unit of measurement (mmHg, kPa, %)
16. If yes: Was there another factor that could have influenced the ETCO_2 level as well? If yes, please answer questions 13–15 for this factor as well.

Section 4 Ventilation mode and default setting

17. Which ventilation mode is currently used most widely at your institution?
18. What are the default settings?
19. Which ventilation mode was most widely used at your institution in 2008?
20. What were the default settings in 2008?

ETCO_2 = end-tidal carbon dioxide.

eTABLE 2 ETCO₂ of the general cohort compared with the subgroups

Variable	Primary cohort	Subgroup	<i>P</i> value †	Subgroup	<i>P</i> value †
	Primary cohort (<i>n</i> = 245,835)	Intracranial cohort	(<i>n</i> = 12,532)	COPD cohort	(<i>n</i> = 1,709)
Median ETCO ₂ (mmHg)	34.00 [32.00–36.00]	32.00 [29.00–34.00]	< 0.001*	34.00 [32.00–37.00]	< 0.001*
TWA-AUC < 3.7 (mmHg *min)	0.00 [0.00–0.00]	0.00 [0.00–25.00]	< 0.001*	0.00 [0.00–2.73]	< 0.001*
TWA-AUC < 4.7 (mmHg *min)	108.98 [22.00–262.21]	295.90 [95.50–775.20]	< 0.001*	118.00 [19.25–309.84]	0.01
TWA-AUC < 6.0 (mmHg *min)	856.0 [487.10–1431.66]	1438.57 [761.68–2610.63]	< 0.001*	1009.28 [559.88–1729.16]	< 0.001*
TWA-AUC > 6.0 (mmHg *min)	0.00 [0.00–0.00]	0.00 [0.00–0.00]	< 0.001*	0.00 [0.00–2.00]	< 0.001*
	Variable	Laparoscopic cohort	(<i>n</i> = 44,526)	Robotic cohort	(<i>n</i> = 12,977)
Median ETCO ₂ (mmHg)		36.00 [34.00–38.00]	< 0.001*	36.00 [33.00–38.00]	< 0.001*
TWA-AUC < 3.7 (mmHg *min)		0.00 [0.00–0.00]	< 0.001*	0.00 [0.00–0.00]	0.49
TWA-AUC < 4.7 (mmHg *min)		47.00 [7.00–145.86]	< 0.001*	97.50 [17.92–287.81]	0.22
TWA-AUC < 6.0 (mmHg *min)		727.46 [409.78–1211.98]	< 0.001*	1413.50 [904.57–1968.29]	< 0.001*
TWA-AUC > 6.0 (mmHg *min)		0.00 [0.00–0.94]	< 0.001*	0.00 [0.00–13.00]	< 0.001*

*Statistically significant at a level of significance of $P < 0.05$. Median values are given with the interquartile range.

†*P* value obtained with a Kruskal-Wallis test, comparing the primary cohort with the subgroup.

COPD = chronic obstructive pulmonary disease; ETCO₂ = end-tidal carbon dioxide; TWA-AUC = time-weighted average area-under-the-curve.

eTABLE 3 Survey results

Institution	Ventilator mode 2008	Volume* 2008 (mL)	Frequency* 2008 (/min)	Ventilator mode 2016	Volume * 2016 (mL)	Frequency * 2016 (/min)	Change in RMV §	Change ETCO ₂ (mmHg)
1	Controlled†	500	12	Controlled	480	15	↑	↑ 5
2	Controlled	500	12	Controlled	500	12	-	↑ 2
3	Controlled	500	12	Controlled	500	12	-	-
4	Controlled	600	10	Controlled	600	10	-	-
5	Controlled	600	8	Controlled	600	8	-	-
6	Controlled	10 #	8–10	Controlled	5–7 #	12–16	↓	↑ 5
7	Controlled	600	10	Controlled	440	10	↓	-
8	Controlled	600	10	SIMV ‡	500	12	-	-

* Default settings of ventilator for volume and frequency of ventilation. † Controlled ventilator modes: pressure or volume control, including pressure controlled modes with a guaranteed volume and volume controlled modes with pressure regulation. ‡ Synchronized Intermittent Mandatory Ventilation. § Change in default RMV (respiratory minute volume, mL·min⁻¹), based on reported default settings from 2008 and from 2016. || Assumed change in ETCO₂ (mmHg) on average, reported by the institution. # Default volume in ml/kg instead of mL.

Institution 1 assumed an increase in ETCO₂ of 5 mmHg as of March 2015 due to implementation of a new ventilator mode with different default settings (namely a pressure regulated volume controlled mode based on lean body mass and age). Institution 2 assumed an increase in ETCO₂ of 2 mmHg as of July 2014 due to an increased use of pressure support modes in addition to emerging evidence for lung protective ventilation strategies. Institution 5 reported a target of 35–40 mmHg for patients receiving colorectal procedures, implemented in November 2013. Institution 6 assumed that the ETCO₂ increased by 5 mmHg since January 2012 because of multiple factors that could not be further defined. Institution 8 reported a major shift in ETCO₂ in 2007 (prior to the study period) after implementation of ventilators with pressure support mode. ETCO₂ = end-tidal carbon dioxide; SIMV = synchronized intermittent mandatory ventilation.

eTABLE 4 Baseline characteristics by ETCO₂ percentile

	Median ETCO₂ < 5th Percentile (n = 7,699)	Median ETCO₂ within 5th – 95th Percentile (n = 226,174)	Median ETCO₂ > 95th Percentile (n = 11,852)	P-Value
Age (yr) *	55 [42-67]	51 [38-63]	48 [34-59]	<0.001 ^{abc}
Sex (female) †	4863 (63.2)	115570 (51.1)	4349 (36.7)	<0.001 ^{abc}
ASA physical status †				<0.001 ^{abc}
I	580 (7.5)	25665 (11.4)	1493 (12.6)	
II	3371 (43.8)	116215 (51.9)	5902 (49.8)	
III	3225 (41.9)	77626 (34.3)	3984 (33.6)	
IV	509 (6.6)	6625 (2.9)	469 (4.0)	
V	14 (0.2)	43 (0.02)	4 (0.03)	
Height (cm) *	167 [160-175]	170 [163-178]	175 [165-182]	<0.001 ^{abc}
BMI (kg·m⁻²) *	26.8 [23.4-31.0]	27.8 [24.1-32.7]	29.3 [24.8-35.4]	<0.001 ^{abc}
Median RMV (mL·min⁻¹) *	5544 [4554-6635]	5592 [4684-6600]	5175 [4212- 6292]	<0.001 ^{abc}
Mean MAP (mmHg)*	78 [72-85]	78 [72-85]	78 [71-86]	<0.001 ^{bc}
Duration of general anesthesia (min) *	161 [122-226]	172 [130-234]	148 [112-200]	<0.001 ^{abc}
Duration of surgery (min) *	88 [61-135]	104 [71-157]	89[60-137]	<0.001 ^{ac}

ASA = American Society of Anaesthesiologist; BMI = body mass index; MAP = mean arterial pressure; RMV = respiratory minute ventilation.

*Median [interquartile range]; †Count and % *P* values reported are for the difference between the three groups. Pairwise *P* values were computed with a = *P* < 0.05 for the difference between the < 5th percentile and the 5-95th percentile, b = *P* < 0.05 for the difference between the < 5th percentile and the >95th percentile, and c = *P* < 0.05 for the difference between the 5th-95th percentile and the >95th percentile.

5th percentile = 29 mmHg, 95th percentile = 41 mmHg. ETCO₂ = end-tidal carbon dioxide.