



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

Étude observationnelle sur les tendances des valeurs du dioxyde de carbone en fin d'expiration au cours de l'anesthésie générale

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Abstract

Purpose Despite growing evidence supporting the potential benefits of higher end-tidal carbon dioxide (ETCO₂) levels in surgical patients, there is still insufficient data to formulate guidelines for ideal intraoperative ETCO₂ targets. As it is unclear which intraoperative ETCO₂ levels are currently used and whether these levels have changed over time, we

investigated the practice pattern using the Multicenter Perioperative Outcomes Group database.

Methods This retrospective, observational, multicentre study included 317,445 adult patients who received general anesthesia for non-cardiothoracic procedures between January 2008 and September 2016. The primary outcome was a time-weighted average area-under-the-curve (TWA-AUC) for four ETCO₂ thresholds (< 28, < 35, < 45, and > 45 mmHg). Additionally, a median ETCO₂ was studied. A Kruskal-Wallis test was used to analyse differences between years. Random-effect multivariable logistic regression models were constructed to study variability.

Presentation: Preliminary data for this study were presented as a poster at the American Society of Anesthesiologists Annual Meeting on October 22, 2017 in Boston.

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Results Both TWA-AUC and median $ETCO_2$ showed a minimal increase in $ETCO_2$ over time, with a median [interquartile range] $ETCO_2$ of 33 [31.0–35.0] mmHg in 2008 and 35 [33.0–38.0] mmHg in 2016 ($P < 0.001$). A large inter-hospital and inter-provider variability in $ETCO_2$ were observed after adjustment for patient characteristics, ventilation parameters, and intraoperative blood pressure (intra-class correlation coefficient 0.36; 95% confidence interval, 0.18 to 0.58).

Conclusions Between 2008 and 2016, intraoperative $ETCO_2$ values did not change in a clinically important manner. Interestingly, we found a large inter-hospital and inter-provider variability in $ETCO_2$ throughout the study period, possibly indicating a broad range of tolerance for $ETCO_2$, or a lack of evidence to support a specific targeted range. Clinical outcomes were not assessed in this study and they should be the focus of future research.

Résumé

Objectif Malgré une accumulation de données probantes suggérant des avantages de taux plus élevés de dioxyde de carbone en fin d'expiration ($ETCO_2$) chez les patients chirurgicaux, nous ne disposons pas encore d'assez de données pour formuler des lignes directrices sur les cibles peropératoires idéales de l' $ETCO_2$. Comme nous ne savons effectivement pas avec certitude quels taux peropératoires d' $ETCO_2$ sont actuellement utilisés et si ces taux ont changé au fil du temps, nous avons étudié l'évolution de la pratique en utilisant la base de données du MPOG (Multicenter Perioperative Outcomes Group).

Méthodes Cette étude multicentrique rétrospective observationnelle a inclus 317 445 patients adultes ayant reçu une anesthésie générale pour des procédures non cardiothoraciques entre janvier 2008 et septembre 2016. Le critère d'évaluation principal était une aire sous la courbe moyenne pondérée en fonction du temps (ASC-mT) pour quatre seuils d' $ETCO_2$ (< 28 , < 35 , < 45 et > 45 mmHg). De plus, une $ETCO_2$ médiane a été étudiée. Un test de Kruskal-Wallis a permis d'analyser les différences entre les années. Des modèles de régression logistique multifactorielle à effet aléatoire ont été construits pour étudier la variabilité.

Résultats L'ASC-mT et l' $ETCO_2$ médiane ont montré une augmentation minime de l' $ETCO_2$ au fil du temps, avec une valeur médiane [plage interquartile] de l' $ETCO_2$ de 33 [31,0 à 35,0] mmHg en 2008 et 35 [33,0 à 38,0] mmHg en 2016 ($P < 0,001$). Une grande variabilité entre les hôpitaux et prestataires de l' $ETCO_2$ a été observée après ajustement pour les caractéristiques des patients, les paramètres de ventilation et la pression artérielle peropératoire (coefficient de corrélation intracatégorie : 0,36; intervalle de confiance à 95 % : 0,18 à 0,58).

Conclusions Entre 2008 et 2016, les valeurs peropératoires de l' $ETCO_2$ n'ont pas varié d'une manière importante sur le plan clinique. Il est intéressant de noter que nous avons trouvé une grande variabilité de l' $ETCO_2$ entre hôpitaux et prestataires tout au long de la période d'étude témoignant peut-être d'une vaste plage de tolérance de l' $ETCO_2$ ou d'un manque de données probantes pour soutenir une valeur cible spécifique. L'évolution clinique n'a pas été analysée au cours de cette étude et elle devra être le centre d'intérêt de futures recherches.

Historically, it has been common practice to maintain hypocapnia (arterial carbon dioxide pressure ($PaCO_2$) < 35 mmHg) during general anesthesia.^{1,2} Intraoperative end-tidal carbon dioxide ($ETCO_2$) values around 30 mmHg were frequently targeted, as hypercapnia ($PaCO_2 > 45$ mmHg) was considered to contribute to intraoperative tachycardia and hypertension, thereby increasing the oxygen demand of the myocardium.^{1,3} In contrast, hypocapnia reduced the need for muscle relaxants and additional anesthetics to prevent spontaneous ventilation. Nevertheless, there is no good evidence to support the benefit of hypocapnia, and some studies suggest benefits for higher $ETCO_2$ levels.^{1,4,5} First, it is easier to implement low tidal volume ventilation.^{6,7} Second, hypercapnia increases the cardiac output, resulting in an increase in tissue oxygenation, which in turn may prevent surgical site infections.^{1,8-10} Third, studies using different lung injury models have shown that hypercapnia has protective, immune-modulating properties that decrease the inflammatory response.¹¹⁻¹³ Fourth, hypercapnia may increase lung parenchymal compliance¹³⁻¹⁵ and can improve ventilation-perfusion matching in the lungs.^{1,12,16} Finally, normocapnia positively influences the neurologic outcome because of vasoactive properties of $PaCO_2$, which is especially pronounced in already injured brains.¹⁷

Unfortunately, many studies focus on the critical care population, leaving surgical patients underrepresented.^{1,2,4,5,8-10} Therefore, there is no strong evidence of a benefit for higher CO_2 tensions compared with hypocapnia in perioperative patients.

To generate evidence to formulate guidelines on $ETCO_2$ management during general anesthesia, we first need to understand current clinical practice. To our knowledge, it is unclear which target $ETCO_2$ levels are currently used and whether these levels have changed over time. Therefore, this study aimed to investigate the practice pattern of $ETCO_2$ levels over time in non-cardiothoracic surgery. We did not aim to study clinical outcomes. We hypothesized

that the target ET_{CO₂} level may have increased over time in response to the existing evidence described above. To further explore the practice pattern, we aimed to investigate four subgroups separately: patients with chronic obstructive pulmonary disease (COPD; subgroup 1); patients undergoing intracranial or carotid artery surgery (subgroup 2); and patients receiving laparoscopic surgery with (subgroup 3) or without (subgroup 4) robot assistance.

Methods

For this multicentre, retrospective, observational study, we used data from the Multicentre Perioperative Outcomes Group (MPOG) database. The MPOG registry, data entry process, and validation of data have been described in detail previously.^{18,19} In brief, MPOG is a consortium of 47 hospitals in North America and Europe, collecting perioperative data to facilitate outcomes research. Institutional Review Board (IRB) approval for MPOG was obtained from the University of Michigan Health System, MPOG's coordinating institution. Each participating institution has separate IRB approval to submit a limited set of perioperative data into the centralized database for future use, without any direct patient identifiers. Ethical approval for the current study was provided by the University Medical Center Utrecht, the leading institution for this project (May 2016, Number 16-282/C). The requirement for written informed consent was waived. No additional IRB approval was sought from other institutions. Additionally, the study protocol was reviewed *a priori* and approved by the MPOG Perioperative Clinical Research Committee (PCRC-0032, September 2016).

Patients

This study included all adult patients ≥ 18 yr who received general anesthesia between 1 January, 2008 and 9 January, 2016 at eight academic institutions affiliated with MPOG: University of Michigan Health System, Ann Arbor, Michigan; Oregon Health & Science University, Portland, Oregon; University of Oklahoma Health Sciences Center, Oklahoma City, OK; Washington University School of Medicine, St. Louis, MO; University of Vermont Medical Center, Burlington, VT; Vanderbilt University, Nashville, TN; University Medical Center Utrecht, Utrecht, the Netherlands; and University of Pennsylvania Health System, Philadelphia, PA, USA. Only institutions submitting data for all variables mentioned below were selected for this study. For patients who received general anesthesia more than once within 30 days, only the first case was included. Exclusion criteria are presented in

Fig. 1. These criteria were based on procedure type, a poor clinical condition prior to anesthesia, and suspected intraoperative hemodynamic instability to limit the risk of artifacts and invalid ET_{CO₂} values. Vasopressor use per hour was used as a proxy for hemodynamic instability. Additionally, we excluded patients who received one-lung ventilation and ventilation by means of a laryngeal mask airway. To ensure sufficient time for data collection, cases with < 40 min between incision and the end of the surgical procedure were excluded. Furthermore, patients with < 20 valid machine-generated ET_{CO₂} measurements were excluded.

A priori, we defined four subgroups of patients in whom the target ET_{CO₂} level was considered to possibly differ from other patients: 1) patients with COPD, as their awake PaCO₂ level may be increased and therefore a higher ET_{CO₂} may be accepted²⁰; 2) patients undergoing intracranial and carotid artery surgery, as these interventions may compromise cerebral perfusion and therefore warrant a strict control of ET_{CO₂},^{1,17} and patients receiving laparoscopic surgery with or without robot assistance (subgroups 3 and 4 respectively), as insufflation with carbon dioxide can increase the PaCO₂, therefore higher ET_{CO₂} levels may need to be tolerated.²¹⁻²³ We differentiated between laparoscopic surgery with and without robot assistance, since Trendelenburg positioning can further increase the PaCO₂.²² All four subgroups were excluded from the primary analysis to avoid confounding the observed change in ET_{CO₂} levels over time, especially because of an increasing utilization of laparoscopic over open procedures. Patients eligible for multiple groups were excluded from all analyses.

Outcome

The primary outcome was ET_{CO₂} stratified into four groups (< 28 , < 35 , < 45 , and > 45 mmHg) and the area-under-the-curve for each specific threshold was estimated with adjustment for the total measurement time, resulting in a time-weighted average area-under-the-curve (TWA-AUC) per threshold. Patients could be binned into multiple groups. Patients with at least one valid ET_{CO₂} < 28 mmHg were binned into the < 28 mmHg group, but these data were also used for the < 35 mmHg and < 45 mmHg groups, respectively. If patients also had at least one valid ET_{CO₂} value > 45 mmHg, the corresponding TWA-AUC was binned into the > 45 mmHg group.

To aid interpretation and clinical applicability, a median ET_{CO₂} per case was obtained as a secondary outcome measure. *A priori*, a relative change of 10% in median ET_{CO₂} over the entire study period was considered to be clinically relevant.

Data collection

Data collection for intraoperative variables started ten minutes after surgical incision to ignore hyper- and hypocapnia that may follow mask ventilation and intubation during induction of anesthesia, and to allow the ETCO_2 to reach a set level. Data collection ended ten minutes prior to the end of the surgical dressing to ignore increased values of ETCO_2 that may be accepted to establish spontaneous ventilation. When the exact incision time was not registered, data collection started 20 min after anesthesia induction. Only valid ETCO_2 values were used (see Table 1S, available as Electronic Supplementary Material for the artifact filter). Data were collected for ventilation parameters (tidal volume, respiratory rate, positive-end-expiratory pressure (PEEP), respiratory minute volume (RMV)) and mean arterial blood pressure (MAP) as potential confounders. Mean arterial pressure and ventilation parameters, including ETCO_2 , were measured continuously during general anesthesia by automated interfaces. An average of these results was recorded every minute in the anesthesia record-keeping system and stored in the centralized MPOG database.

Preoperative data on sex, height, body mass index (BMI), age, and American Society of Anesthesiologists (ASA) physical status were collected as covariates.²⁴ For every case, we recorded the institution and determined the primary anesthesia provider, defined as the supervising anesthesiology faculty and primary anesthesia caregiver (either nurse anesthetist or resident) that provided anesthesia for at least 75% of the time.

Statistical analysis

Descriptive statistics were computed using frequencies and percentages for categorical variables and medians with interquartile ranges [IQR] for continuous data after checking continuous variables for normality using the Kolmogorov-Smirnov test.

Differences in baseline characteristics, ventilation parameters, and mean MAP between the primary cohort and the subgroups and between the beginning and end of the study were analyzed using a Kruskal-Wallis test.

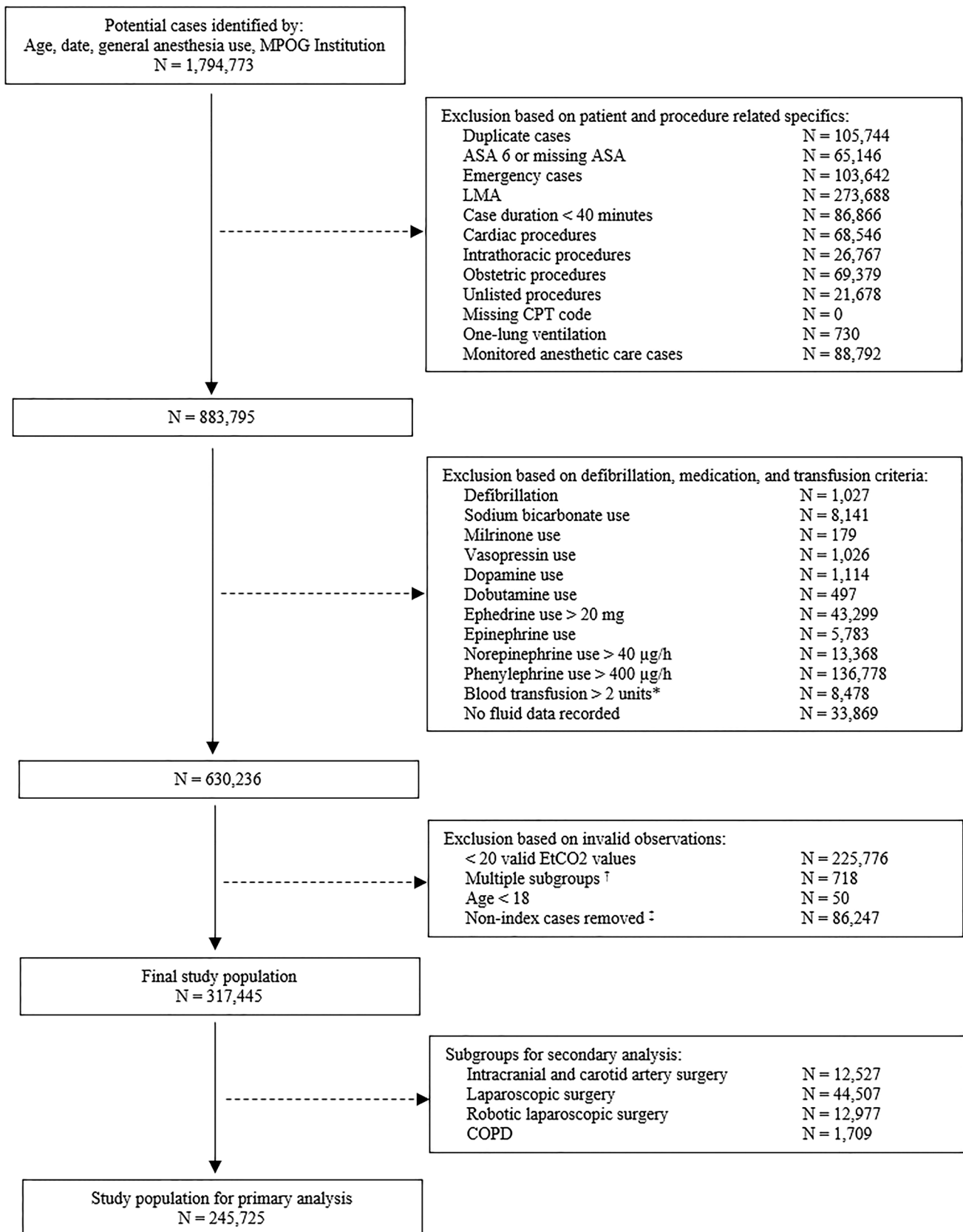
For all four thresholds, the TWA-AUC of each patient was computed from minute-level ETCO_2 values using a fitted cubic spline curve (see Figure available as Electronic Supplementary Material showing the method to calculate the area-under-the-curve). For every case, a median was calculated for tidal volume, respiratory rate, PEEP, and RMV. We determined the mean MAP for every case, as a summary measure for the overall blood pressure.

Fig. 1 Flow chart. ASA = American Society of Anesthesiologist; CPT = current procedural terminology; ETCO_2 = end-tidal carbon dioxide. LMA = laryngeal mask airway; MPOG = Multicenter Perioperative Outcomes Group. *Blood transfusion > two units was defined as: more than two units of packed cells or whole blood or more than 600 mL of cell saver blood during general anesthesia. † Patients were excluded when they met the inclusion criteria of more than one subgroup: e.g., chronic obstructive pulmonary disease (COPD) and laparoscopic surgery. ‡ Only the first case within 30 days was included

Both the TWA-AUC and median ETCO_2 were plotted over time and values were compared between years using a Kruskal-Wallis test. Medians and IQR were reported.

Prior to the start of this study, we surveyed all participating centres to gain insight into target ETCO_2 levels and factors that might have influenced these levels during the study period. The full survey can be found in the Supplemental Material. When abrupt changes in ETCO_2 were reported by at least half of all institutions, an interrupted time series (ITS) analysis was considered.

To examine variation in ETCO_2 , patient characteristics were compared between patients with a median ETCO_2 < 5th percentile, between the 5th and 95th percentile, and > 95th percentile using a Kruskal-Wallis test. To examine variation between and within each institution, six mixed-effect multivariable logistic regression models were built. A positive TWA-AUC ETCO_2 > 45 mmHg (meaning that at least one ETCO_2 value per case was > 45 mmHg) was used as a binary outcome measure in all models. Before any regression models were constructed, all variables under consideration for model inclusion were checked for collinearity using the condition index. If the condition index was > 30, a Pearson's correlation matrix was developed. Those variables deemed to be collinear (defined as a correlation of ≥ 0.70) were either combined into a single variable or removed. All non-collinear variables were entered into the models. The included fixed effects were selected based upon clinical relevance: age (binned per decade, reference group 18–30), sex, BMI (binned into < 18.5, 18.5–24.9 (reference group), 25.0–29.9, 30.0–34.9, 35.0–39.9, $\geq 40.0 \text{ kg}\cdot\text{m}^{-2}$), ASA class (I or II vs III, IV, V), median tidal volume (binned by ideal body weight into < 6, 6–8 (reference group), 8–10, > 10 $\text{mL}\cdot\text{kg}^{-1}$), median respiratory rate (binned into < 12, 12–16 (reference group), 16–20, > 20 min^{-1}), median PEEP (binary, < 5 or $\geq 5 \text{ cmH}_2\text{O}$), mean MAP (< 65, 65–80 (reference group), > 80 mmHg), and year of the procedure. All six mixed-effects models contained the same fixed effects with differing random effects between the models. The first model used institution as a random effect to examine the variation between institutions; the second model used primary anesthesia caregiver, and the third used supervising



anesthesiology faculty as random effects to examine how much of the variation could be explained by inter-provider variability. The fourth model used supervising anesthesiology faculty nested within institution as a random effect and the fifth model used primary anesthesia caregiver nested within institution to further explore variation due to preferences of a provider within a specific institution. The final model was built with primary anesthesia caregiver nested within supervising anesthesiology faculty, which was again nested within institution, as the random effect. This model was built to explore how much of the variation could be explained by a particular anesthesia care team in a specific institution. Measures of effect size for random effects were reported as intraclass correlation coefficients (ICC) and median odds ratios (MOR) with corresponding 95% confidence intervals (CI).²⁵

All analyses were conducted for the general cohort and the subgroups separately. A *P* value of 0.05 was considered statistically significant for all analyses.

The analyses were conducted using SAS v. 9.4 (SAS Institute, Cary, NC, USA) and Stata v. 13.1 (StataCorp

LLC; College Station, TX, USA). The study was conducted in adherence to the STROBE statement for observational research.²⁶

Results

One million, seven hundred and ninety-four thousand, seven hundred and seventy-three patients met the initial inclusion criteria of general anesthesia and age. After application of all *a priori* defined exclusion criteria and after exclusion of invalid observations, 317,445 patients were eligible. We included 245,725 patients in our primary analysis and 71,720 patients in different subgroups (Fig. 1). Patient characteristics for the primary cohort and the subgroups are described in Table 1. Additionally, differences in patient characteristics between 2008 and 2016 are shown in Table 2. Over time, patients were slightly older, had a higher BMI, and had a higher ASA class. RMV slightly decreased over time, whereas the mean MAP increased over time. The duration of both the procedure and general anesthesia decreased over time.

Table 1 Baseline characteristics for the general cohort and the subgroups

	General cohort (<i>n</i> = 245,725)	Intracranial and carotid artery surgery (<i>n</i> = 12,527)	Laparoscopic surgery (<i>n</i> = 44,507)	Robotic laparoscopic surgery (<i>n</i> = 12,977)	COPD (<i>n</i> = 1709)
Age (yr)*	51 [38–63]	53 [39–64]	49 [36–60]	60 [52–66]	65 [55–73]
Sex (female)†	124782 (50.8)	6442 (51.4)	28661 (64.4)	3364 (25.9)	810 (47.40)
ASA physical status†	27738 (11.3)	735 (5.9)	4494 (10.1)	513 (4.0)	0 (0.0)
I	125488 (51.1)	4736 (37.8)	23039 (51.8)	7705 (59.4)	341 (20.0)
II	84835 (34.5)	6447 (51.5)	16351 (36.7)	4667 (36.0)	1173 (68.6)
III	7603 (3.1)	598 (4.8)	622 (1.4)	92 (0.7)	192 (11.2)
IV	61 (0.02)	11 (0.1)	1 (0.0)	0 (0.0)	3 (0.2)
V					
Height (cm)*	170 [163–178]	170 [163–178]	168 [162–175]	175 [168–182]	170 [160–178]
BMI (kg·m ⁻²)*	27.8 [24.1–32.7]	27.3 [23.8–31.7]	29.8 [25.1–37.3]	28.7 [25.6–32.6]	27.2 [23.4–32.6]
Median RMV (mL·min ⁻¹)*	5571 [4660–6590]	6012 [4960–7238]	6288[5391–7330]	6720 [5860–7692]	5560 [4728–6504]
Median respiratory rate*	10 [9–12]	12 [10–13]	12 [10–14]	12 [10–14]	10 [9–12]
Median ETCO ₂ (mmHg)*	34.0 [32.0–36.0]	32.0 [29.0–34.0]	36.0 [34.0–38.0]	36.0 [33.0–38.0]	34.0 [32.0–37.0]
Mean MAP (mmHg)*	78 [72–85]	81 [75–87]	82 [76–89]	83 [77–89]	80 [74–86]
Duration of general anesthesia (min)*	170 [129–232]	233 [173–325]	167 [126–225]	251 [213–301]	197 [150–265]
Duration of surgery (min)*	103 [70–155]	133 [84–211]	106 [72–153]	179 [145–226]	122 [83–186]

*Median [interquartile range]; †Count and %

ASA = American Society of Anesthesiologist; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ETCO₂ = end-tidal carbon dioxide; MAP = mean arterial pressure; RMV = respiratory minute ventilation

Table 2 Baseline characteristics and ET_{CO₂} levels for 2008 and 2016

	Case year 2008 (<i>n</i> = 23434)	Case year 2016 (<i>n</i> = 18797)	<i>P</i> Value
General cohort			
Age (yr)†	50 [38–62]	52 [37–64]	< 0.001*
Sex (female)‡	11922 (50.9)	9511 (50.6)	< 0.001*
ASA physical status‡			< 0.001*
I	3148 (13.4)	1965 (10.5)	
II	12477 (53.2)	9209 (49.0)	
III	7130 (30.4)	6986 (37.2)	
IV	672 (2.9)	632 (3.4)	
V	7 (0.03)	5 (0.03)	
Height (cm)†	170 [163–178]	170 [163–178]	0.14
BMI (kg·m ⁻²)†	27.4 [23.9–32.1]	28.09 [24.2–33.1]	< 0.001
Median RMV (mL·min ⁻¹)†	5665 [4744–6708]	5480 [4572–6468]	< 0.001
Mean MAP†	77 [71–84]	80 [73–86]	< 0.001
Duration of general anesthesia (min)†	178 [134–241]	167 [127–224]	< 0.001
Duration of surgery (min)†	106 [72–160]	102 [69–153]	< 0.001*
TWA-AUC ET _{CO₂} < 28 mmHg	0.0 [0.0–1.0]	0.0 [0.0–0.0]	< 0.001*
TWA-AUC ET _{CO₂} < 35 mmHg	169.0 [57.8–351.8]	45.4 [2.0–161.9]	< 0.001*
TWA-AUC ET _{CO₂} < 45 mmHg	986.9 [573.5–1621.8]	713.2 [385.0–1218.1]	< 0.001*
TWA-AUC ET _{CO₂} > 45 mmHg	0.0 [0.0–0.0]	0.0 [0.0–2.73]	< 0.001*
Median ET _{CO₂} (mmHg)	33.0 [31.0–35.0]	35.0 [33.0–38.0]	< 0.001*
Intracranial and carotid artery surgery†			
TWA-AUC ET _{CO₂} < 28 mmHg	0.0 [0.0–35.0]	0.0 [0.0–17.0]	0.03*
TWA-AUC ET _{CO₂} < 35 mmHg	376.5 [145.0–812.5]	181.0 [28.4–658.3]	< 0.001*
TWA-AUC ET _{CO₂} < 45 mmHg	1581.3 [841.5–2680.7]	1238.9 [622.1–2292.3]	< 0.001*
TWA-AUC ET _{CO₂} > 45 mmHg	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.001*
Median ET _{CO₂} (mmHg)	31.6 [29.0–33.0]	33.0 [30.0–36.0]	< 0.001*
Laparoscopic surgery†			
TWA-AUC ET _{CO₂} < 28 mmHg	0.0 [0.0–0.0]	0.0 [0.0–0.0]	< 0.001*
TWA-AUC ET _{CO₂} < 35 mmHg	76.3 [19.0–193.3]	17.3 [0.34–77.1]	< 0.001*
TWA-AUC ET _{CO₂} < 45 mmHg	856.9 [489.7–1408.2]	574.0 [327.5–990.2]	< 0.001*
TWA-AUC ET _{CO₂} > 45 mmHg	0.0 [0.0 to 1.0]	0.0 [0.0–3.58]	< 0.001*
Median ET _{CO₂} (mmHg)	35.0 [33.0–37.0]	37.0 [35.0–40.0]	< 0.001*
Robotic laparoscopic surgery†			
TWA-AUC ET _{CO₂} < 28 mmHg	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.03*
TWA-AUC ET _{CO₂} < 35 mmHg	140.2 [31.9–327.9]	58.5 [7.0–187.0]	< 0.001*
TWA-AUC ET _{CO₂} < 45 mmHg	1538.9 [1099.0–2028.5]	1306.3 [849.1–1884.4]	< 0.001*
TWA-AUC ET _{CO₂} > 45 mmHg	0.0 [0.0–4.0]	0.0 [0.0–19.0]	< 0.001*
Median ET _{CO₂} (mmHg)	35.0 [33.0–37.7]	37.0 [35.0–39.0]	< 0.001*
COPD†			
TWA-AUC ET _{CO₂} < 28 mmHg	0.0 [0.0–2.0]	0.0 [0.0–0.0]	0.06
TWA-AUC ET _{CO₂} < 35 mmHg	162.4 [41.3–394.0]	22.8 [1.5–164.5]	< 0.001*
TWA-AUC ET _{CO₂} < 45 mmHg	1151.0 [658.0–1989.1]	728.9 [390.4–1264.8]	< 0.001*
TWA-AUC ET _{CO₂} > 45 mmHg	0.0 [0.0–0.24]	0.0 [0.0–21.6]	< 0.001*
Median ET _{CO₂} (mmHg)	34.0 [32.0–36.0]	36.0 [34.0–39.0]	< 0.001*

*Statistically significant at a level of significance of $P < 0.05$ †Median [interquartile range]. ‡Count and %

ASA = American Society of Anesthesiologist; BMI = body mass index; COPD = chronic obstructive pulmonary disease. ET_{CO₂} = end-tidal carbon dioxide; MAP = mean arterial pressure; RMV = respiratory minute ventilation; TWA-AUC = time-weighted average area-under-the-curve

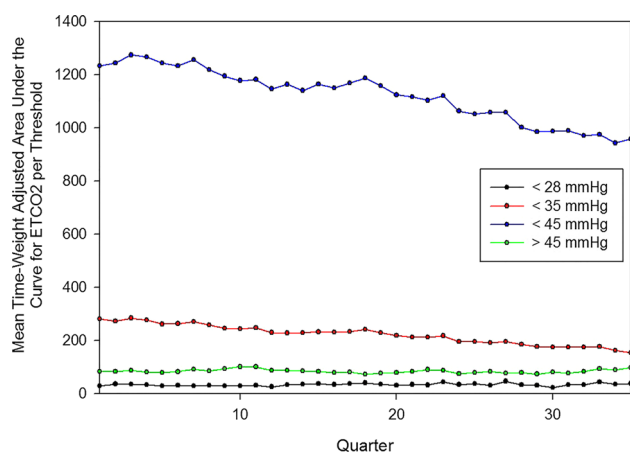


Fig. 2 Trend in TWA-AUC ETCO₂ for four different thresholds. The trend over time in mean time-weighted average area-under-the-curve (TWA-AUC) per quarter for an end-tidal carbon dioxide levels (ETCO₂) of < 28 mmHg, < 35 mmHg, < 45 mmHg, and > 45 mmHg. The TWA-AUC decreased over time for an ETCO₂ threshold of < 28, < 35, and < 45 mmHg, whereas the TWA-AUC ETCO₂ > 45 mmHg increased over time

Change in ETCO₂ over time

The mean TWA-AUC per quarter of a year was plotted for all four ETCO₂ thresholds (Fig. 2, data for the general cohort) and showed that more time was spent closer to or above the threshold of 45 mmHg. There was a statistically significant decrease in TWA-AUC from 2008 to 2016 for an ETCO₂ < 28 mmHg, < 35 mmHg, and < 45 mmHg, whereas a TWA-AUC ETCO₂ > 45 mmHg significantly increased over time (Table 2). The median [IQR] ETCO₂ was plotted over time (Fig. 3a) and showed a minimal increase from 33 [31.0–35.0] mmHg in 2008 to 35 [33.0–38.0] mmHg ($P < 0.001$) in 2016.

Similar trends were obtained for the subgroups over time (Fig. 3 and Table 2). Nevertheless, the ETCO₂ was lower for patients presenting for intracranial and carotid artery surgery and higher for patients in the (robotic) laparoscopic cohort and for patients with COPD (see also Table 2S, available as Electronic Supplementary Material, showing the median ETCO₂ and TWA-AUC per threshold for the general cohort and all subgroups).

In the survey, two out of eight (25%) institutions reported a decrease in RMV between 2008 and 2016, and one institution (12.5%) reported an increase in RMV. Three institutions (37.5%) reported an increase in target ETCO₂ level varying between 2 and 5 mmHg. Since a minority of institutions reported a change in time, we refrained from conducting ITS analysis. Results from the survey are summarized in Table 3S in the Electronic Supplementary Material.

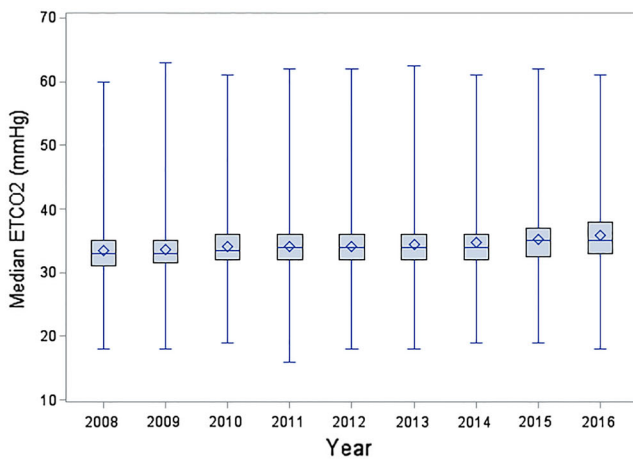
Variation in ETCO₂

The median ETCO₂ plots showed a large spread between the 10th and 90th percentile (Fig. 3). Characteristics of patients with a median ETCO₂ < 5th percentile (< 29 mmHg), between the 5th and 95th percentile (29–41 mmHg), and > 95th percentile (41 mmHg) were compared (see Table 4S available as Electronic Supplementary Material showing the baseline characteristics by percentile). Patients with a higher median ETCO₂ were, on average, younger, had a higher BMI, a lower ASA class, and were more often male. The median RMV was lower for patients with a higher median ETCO₂. The duration of both general anesthesia and surgery was longest for patients with an intermediate ETCO₂ (between 29 and 41 mmHg).

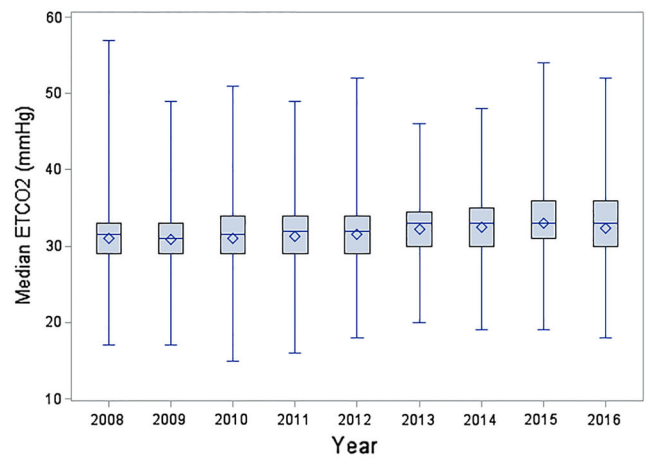
After adjusting for patient characteristics, ventilation parameters, and mean MAP, an ICC of 0.18 (95% CI, 0.07 to 0.37) was found for a model using institution as a random effect, 0.17 (95% CI, 0.16 to 0.19) for a model with primary anesthesia caregiver as a random effect, and 0.12 (95% CI, 0.11 to 0.14) for a model with supervising anesthesiology faculty as a random effect (Table 3). An ICC of 0.36 (95% CI, 0.18 to 0.58) was found for a model with primary anesthesia caregiver nested within a specific supervising anesthesiology faculty, nested within a specific institution, as a random effect. This corresponded with a MOR of 1.98 (95% CI, 1.90 to 2.07). In this, the MOR can be interpreted as the median increase in the odds of having at least one ETCO₂ value per case > 45 mmHg, when an individual moves from a one cluster to another. The subgroup consisting of patients with COPD was too small to conduct random-effect multivariable logistic regression models.

Discussion

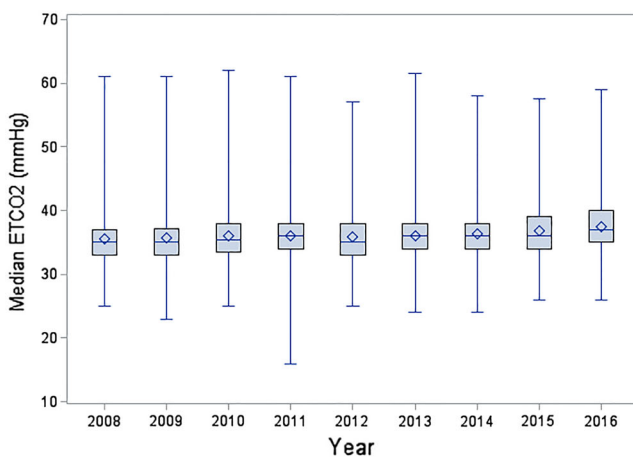
Between 2008 and 2016, median ETCO₂ levels increased minimally, but this change did not meet the *a priori*-defined clinically relevant threshold of 10%. A large variation in target ETCO₂ levels was observed between institutions and between providers for the general cohort and all subgroups. Interestingly, only a minority of this variation could be attributed to the institution and anesthesia provider, while controlling for patient characteristics. The amount of variability that could be attributed to institution and primary anesthesia caregiver was overall slightly larger than the amount that could be attributed to the supervising anesthesiology faculty, except for intracranial and carotid artery surgery, where the preference of the supervising anesthesiology faculty



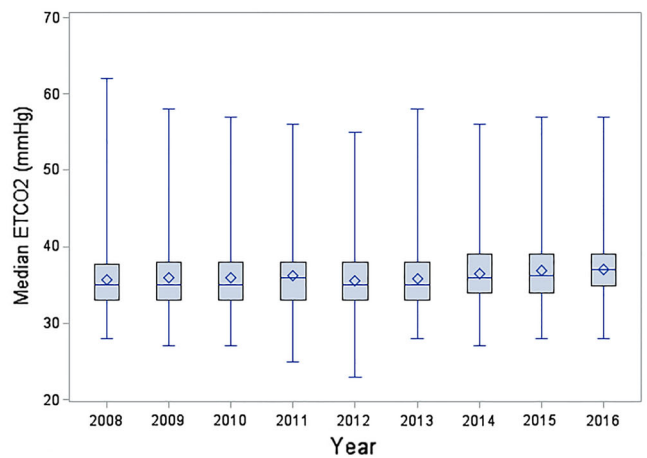
A General Cohort



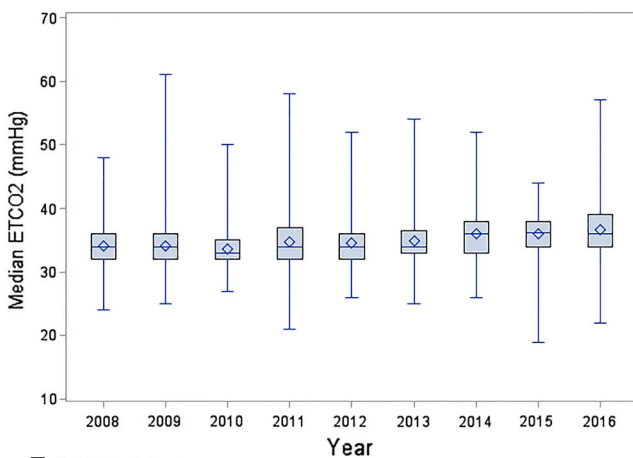
B Intracranial and Carotid Artery Surgery



C Laparoscopic Surgery Cohort



D Robotic Laparoscopic Surgery Cohort



E COPD Cohort

Fig. 3 Trend in median ETCO₂ over time. The boxplots show an increase in median end-tidal carbon dioxide (ETCO₂) values between 2008 and 2016 for the general cohort (A) and the subgroups (B–E). The triangle represents the mean, the whiskers represent the spread between the 10th and 90th percentile. The median ETCO₂ was lower

for patients presenting for intracranial and carotid artery surgery (B) compared with the general cohort. The median ETCO₂ was higher for patients in the (robotic) laparoscopic cohort (C, D) and for patients with chronic obstructive pulmonary disease (COPD) (E) compared with the general cohort (A)

Table 3 Institutional and provider variation

Random effect per model*		General cohort <i>n</i> = 245,725	Intracranial and carotid artery surgery <i>n</i> = 12,527	Laparoscopic surgery <i>n</i> = 44,507	Robotic laparoscopic surgery <i>n</i> = 12,977
Institution	ICC (95% CI)	0.18 (0.07–0.37)	0.14 (0.05–0.33)	0.11 (0.04–0.26)	0.22 (0.09–0.44)
	MOR (95% CI)	1.96 (1.28–6.32)	1.66 (1.19–4.55)	1.44 (1.13–2.95)	2.36 (1.34–12.15)
Supervising anesthesiology faculty	ICC (95% CI)	0.12 (0.11–0.14)	0.18 (0.12–0.25)	0.05 (0.04–0.08)	0.19 (0.15–0.24)
	MOR (95% CI)	1.56 (1.45–1.69)	1.96 (1.54–2.84)	1.20 (1.13–1.29)	2.10 (1.75–2.69)
Primary anesthesia caregiver	ICC (95% CI)	0.17 (0.16–0.19)	0.15 (0.10–0.21)	0.14 (0.12–0.16)	0.30 (0.26–0.35)
	MOR (95% CI)	1.91 (1.79–2.06)	1.79 (1.44–2.24)	1.68 (1.55–1.84)	3.86 (2.91–5.51)
Supervising anesthesiology faculty nested within institution	ICC (95% CI)	0.23 (0.09–0.49)	0.22 (0.10–0.40)	0.12 (0.03–0.37)	0.18 (0.05–0.46)
	MOR (95% CI)	1.08 (1.06–1.10)	1.42 (1.23–1.83)	1.12 (1.03–1.42)	1.05 (1.02–1.13)
Primary anesthesia caregiver nested within institution	ICC (95% CI)	<i>Did not converge</i>	0.23 (0.11–4.23)	0.17 (0.08–.31)	0.31 (0.14–0.55)
	MOR (95% CI)		1.34 (1.18–1.68)	1.26 (1.20–1.34)	1.39 (1.26–1.60)
Primary anesthesia caregiver nested within supervising anesthesiology faculty, nested within institution	ICC (95% CI)	0.36 (0.18–0.58)	0.26 (0.12–0.48)	0.27 (0.16–0.42)	0.37 (0.19–0.59)
	MOR (95% CI)	1.98 (1.90–2.07)	1.21 (1.01–31.25)	1.29 (1.16–1.49)	2.06 (1.58–3.12)

*Dependent variable: positive TWA-AUC $\text{ETCO}_2 > 45$ mmHg (yes/no). Fixed effects: age (binned per decade), body mass index (binned into < 18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥ 40.0 $\text{kg}\cdot\text{m}^{-2}$), sex, ASA class (I or II vs III, IV, or V), positive end-expiratory pressure (binary, < 5 or ≥ 5 mmHg), tidal volume (binned by ideal body weight into < 6, 6–8, 8–10, > 10 $\text{mL}\cdot\text{kg}^{-1}$), median respiratory rate (binned into < 12, 12–16, 16–20, $> 20\cdot\text{min}^{-1}$), mean of the mean arterial blood pressure (binned < 65, 65–80, > 80 mmHg) and year of procedure. Random effects differed per model and included institution, primary anesthesia caregiver, and/or attending anesthesiologist

The subgroup of patients with a history of chronic obstructive pulmonary disease was too small to conduct random-effect multivariable logistic regression analyses

CI = confidence interval; ICC = intraclass correlation coefficient; MOR = median odds ratio

seemed to be more important than the effect of institution and primary anesthesia caregiver.

Practice variation in targeted ETCO_2 levels has not been studied previously. Large practice variation across regions, institutions, and physicians is reported throughout the medical field.²⁷ Previously, a variation of 18% in tidal volume was shown to be attributable to institutional variability.²⁴ The same amount of variation could be attributed to institutional variability in our study.

The large variation in ETCO_2 found in this study may have several implications. It raises the question whether anesthesia providers care for any ETCO_2 target at all, or at least it could be theorized that ETCO_2 levels are not as important as maintaining, for example, adequate blood pressure levels or oxygen saturation. Likely, there is insufficient knowledge about the effects of ETCO_2 levels to guide anesthesia providers in targeting specific ETCO_2 levels. We believe further exploration of the effect of intraoperative ETCO_2 levels on postoperative outcome is required to determine what ETCO_2 level should be aimed for to improve patient outcome. This research group has initiated two new projects to study the association between intraoperative ETCO_2 levels and postoperative pulmonary complications, and the association between intraoperative

ETCO_2 levels and neurologic outcome in the neurosurgical population.

As all retrospective analyses, this study has limitations. First, we did not differentiate between spontaneous and controlled ventilation, but we only included cases with endotracheal tubes placed. By excluding cases managed with laryngeal mask airways, the likelihood of spontaneous breathing patterns was reduced significantly. It could be argued that some of the residual spontaneous breathing might lead to a higher ETCO_2 level and that this may explain the observed variation. Nevertheless, we would expect that an unacceptable ETCO_2 level (either hyper- or hypocapnia) would be corrected by the anesthesia provider. Therefore, since the aim of this study was to investigate which levels are being accepted, we did not differentiate between these ventilation methods. Second, the use of certain ventilator modes might be associated with the practice pattern in ETCO_2 levels, e.g., a volume-controlled ventilation mode with a specific default setting, but this was not taken into account in this study. As became apparent from the survey, the majority of institutions used a strictly controlled default ventilation mode. Third, a TWA-AUC is not easily applicable in daily practice. Nevertheless, our primary aim was to investigate the

practice pattern over time for further research purposes and we believe that a median ET_{CO₂} per case would not suffice to summarize a case adequately. Four ranges of ET_{CO₂} and thus four different TWA-AUC values per case allowed us better to summarize a very long case compared with one overall value. The median ET_{CO₂} was added as a secondary outcome measure to aid interpretation and clinical applicability. Fourth, the intraoperative time-frame used for data collection was chosen based upon expert consensus. We aimed to collect data during a relatively stable phase of general anesthesia. We checked timeframes in randomly selected cases and found a good correspondence with the maintenance phase of anesthesia. Finally, although we adjusted the results for a large set of potential confounders, residual confounding might be present because of the retrospective nature of this study.

Conclusion

There was no clinically relevant change in intraoperative ET_{CO₂} levels between 2008 and 2016. Nevertheless, there was a very large practice variation, even within institutions and providers that could not be fully explained by differences in patient or procedure characteristics. Although existing literature suggests that ET_{CO₂} levels of 40 mmHg or higher might be associated with better outcomes in mechanically-ventilated patients,^{4,5,9,17,28} this is not reflected in current clinical anesthesia practice. Clinical outcomes were not assessed in this study and should be the focus of future research to formulate clear guidelines.

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APPENDIX

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