PCRC Proposal Cover Sheet

Title of Study or Project:	An observational study of end-tidal CO2 trends in general anesthesia. A report from the Multicenter Perioperative Outcomes Group
Primary Institution:	University Medical Center Utrecht, The Netherlands.
Principal Investigator:	Wilton van Klei
Co-Investigators:	Annemarie Akkermans (primary author), Judith van Waes, Linda Peelen, Amy Shanks, Aleda Thompson, Leif Saager, Sachin Kheterpal
Type of Study:	☒ Retrospective Observational ☐ Exploratory
IRB Number/Status:	Approved under the University of Michigan and the University Medical Center of Utrecht (WMO waiver)
Hypothesis:	The median end-tidal CO2 level during mechanical ventilation has increased over time, from 28 mmHg to around 45 mmHg.
Number of Patients/Participants:	We expect to include ± 300,000 patients
Power Analysis:	Does not apply
Proposed statistical test/analysis:	A multivariable quantile regression.
Resources (Brief summary of resources for data collection, personnel, financial):	The Multicenter Perioperative Outcomes Group

An observational study of end-tidal CO_2 trends in general anesthesia

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Abstract

Intraoperative ventilation strategies have been subject to change, especially through to the concept of lung protective ventilation. (The Acute Respiratory Distress Syndrome Network) Over the years, the intraoperative tidal volume size has decreased, whereas more patients are receiving PEEP ≥ 5 cm H_2O. (Bender et al.)

We believe that the median end-tidal carbon dioxide level and median respiratory minute ventilation seen in patients under general anesthesia have changed over time as well. However, to our knowledge, this has not been investigated. We are under the impression that the median end-tidal carbon dioxide value has shifted upwards from 28-35 mmHg to normal carbon dioxide levels (35-45 mm Hg). This is probably influenced by emerging evidence reporting the benefits of permissive hypercapnia.(Way and Hill) The purpose of this retrospective observational study is to describe the practice trends in end-tidal carbon dioxide (ETCO2) and respiratory minute ventilation between 2008 and 2016 in several hospitals in North-America and Europe.

Introduction

What is the significance of the clinical problem being addressed?

Over the past years research has shown that the application of low tidal volume ventilation (6ml/kg of predicted body weight (PDW)) is associated with a reduction in lung inflammation and mortality due to acute lung injury and acute respiratory distress syndrome.(Slutsky and Ranieri; The Acute Respiratory Distress Syndrome Network) Lung protective ventilation is a widely accepted method.(Slutsky and Ranieri) Recently, results of a large retrospective study were published, investigating the trends in tidal volume and positive end-expiratory pressure application in surgical patients under general anesthesia. A significant percentage of patients is still ventilated with tidal volumes > 10ml/kg predicted body weight (PBW). However, the median intraoperative tidal volume size has decreased in the past decade. The percentage of patients receiving PEEP ≥ 5 cm H_2O has increased over time. (Bender et al.)

At our institution we have observed that the end-tidal carbon dioxide level (and in combination with that, the respiratory minute ventilation) has been subject to change as well. In the early 2000’s, a median end-tidal carbon dioxide value between 28 and 35 mmHg was not uncommon. It was considered that hypercapnia contributes to intraoperative tachycardia and hypertension, both increasing the oxygen demand of the myocardium, which in turn might lead to myocardial ischemia and infarction. In contrast, hypocapnia reduces the need for muscle relaxants and additional anesthetics to prevent spontaneous ventilation. This led to the assumption that hyperventilation with a low end tidal carbon dioxide level (ETCO2) was preferential. However, there is growing evidence reporting the benefits of permissive hypercapnia. Hypercapnia increases the cardiac output, resulting in an increase in tissue perfusion and oxygenation, strengthened by a shift in the oxyhemoglobin dissociation curve to the right. Mild hypercapnia is also associated with less cognitive dysfunction, as compared to hypocapnia or even normocapnia.(Way and Hill) When allowing a higher ETCO2, it is easier to implement the principle of low tidal volume ventilation. Especially in the field of neuro-anesthesiology, increased attention has been paid to the end-tidal carbon dioxide levels. Both high and low arterial CO2 pressure (PaCO2) might influence the neurological outcome in patients with brain injury to a great extent. (Curley, Kavanagh, and Laffey)

What current gaps exist in the understanding of this problem?

To our knowledge, it is unclear which median end tidal carbon dioxide (ETCO2) levels are currently used in daily practice and which practice pattern can be seen over the years. We will survey all participating centers prior to the start of our project to estimate whether they use a particular target and whether they have observed a shift in ETCO2 level over time. We will ask for possible policy adaptation that might have influenced the practice pattern. We will inquire what this adaptation exactly was and when it occurred. We will also collect current and previous default ventilator settings from all participating centers.

How will does this project address this gap and advance clinical care and/or research knowledge?

Because of the important influence of PaCO2 levels, for example on the cardiovascular system, we believe that it is crucial to gain inside into differences in end-tidal CO2 levels that might have developed over time.(Way and Hill) When we know how the practice pattern changed over time, we can further investigate the potential influence of this change on the postoperative outcome in patients. One interesting sequel study might be the association between hypercapnia and surgical side infection. Hypercapnia is thought to decrease the change of surgical side infections due to increased peripheral perfusion ad oxygenation, however prior research has been un able to come to a definite conclusion. (Ozan Akça et al.; O. Akça et al.)

Methods

IRB statement

Institutional Review Board approval has been obtained from the University of Michigan Health System for this project. Each participating institution that will contribute data has an IRB approval to submit a limited set of perioperative data into the centralized database of the Multicenter Perioperative Outcomes Group, without any direct patient identifiers. No patient care interventions will be done. As principal investigator we obtained a separate IRB approval for this particular study from the University Medical Center of Utrecht (number 16-282/C).

Study type

We propose a retrospective, observational, descriptive study using the Multicenter Perioperative Outcome Group database.

Primary outcome

The primary outcome will be the median intraoperative ETCO2.

Secondary outcome(s), where applicable

Secondary outcomes include the median initial respiratory minute ventilation (between 10 and 15 minutes after incision) and the overall median respiratory minute ventilation, both as a continuous measure. Additionally, we will stratify ETCO2 into four groups (< 28, 28-35, 35-45 and > 45 mmHg) and examine the difference in time-weight adjusted area under the curve ETCO2 (TWA-AUC) between groups. The final secondary outcome will be the difference in median ETCO2 between the beginning of the study period (2008) and the end of the study period (2016). A relative change of 10% between the two time periods will be considered clinically relevant.

Subgroup analyses

We will perform four subgroup analyses:

1. For some interventions, tight CO2 control is of greater importance than for other interventions. Especially interventions that might compromise cerebral perfusion warrant a strict carbon dioxide control.(Curley, Kavanagh, and Laffey; Way and Hill) We will therefore analyze patients receiving intracranial surgery and carotid endarterectomy separately.

2. In patients receiving (robotic assisted) laparoscopic surgery insufflation with CO2 can increase the arterial carbon dioxide content. In these patients, higher end-tidal CO2 levels might be accepted. (Danic et al.; Kalmar et al.; Sood) In our subgroup analyses we will differentiate between laparoscopic surgery with and without robotic assistance, to estimate whether a difference can be found.

3. In patients with chronic obstructive pulmonary disease the arterial and end-tidal CO2 might be increased and again higher levels are likely to be accepted (Dempsey and Smith; Treschan, Malbouisson, and Beiderlinden). We will do a subgroup analysis for this group as well.

We will exclude the three above mentioned groups from our primary analysis to prevent them from confounding the trend over time. Especially due to increased use of laparoscopy and robot-assisted interventions, we believe we would otherwise detect an increase in laparoscopic cases instead of a possible trend in ETCO2 practice pattern.

4. For every case we will estimate who was the primary anesthesia provider (for at least 75% of the time; either the anesthesiologist, the resident or the Certified Registered Nurse Anesthetists). We will estimate the median ETCO2 for every case the anesthesiologist supervised and compare these values. By doing so we would like to estimate whether it is the anesthesiologist or the primary anesthesia provider that determines the end-tidal CO2 level.

Potential confounders

Since Bender et al. found that patients who were obese (BMI >30), female or had a short stature (height < 165cm/65 inches), received higher tidal volumes, we assume that these factors might also influence our data. (Bender et al.) We will correct for these potential confounders. Others possible confounders might be age and ASA physical status.

Another possible confounder might be (a change in) blood pressure variability. For every case, we will make a Shewhart control chart, using the mean arterial blood pressure, collected in the anesthesia record keeping system. We will use invasive blood pressure measurements when available and non-invasive measurements will be used as alternative. We will quantify the variability for every case, using the upper and lower control limit, set at three standard deviations from the mean, by estimating the distance between these two limits. (Montgomery; Tennant et al.) We will not look into a change in prevalence of antihypertensive drug use, since there is very limited data concerning this topic in the MPOG database.

The use of certain ventilator modes might also be associated with a particular practice pattern in ETCO2 levels. Unfortunately, ventilator mode is not well documented in our database and we will not be able to investigate this, other than by means of our survey.

Patient inclusion criteria

For this study, we defined several inclusion criteria:

1. We will include only adult patients (18 years or older)
2. All patients had to receive general anesthesia
   - General anesthesia is defined as documented use of mask or endotracheal tube, administration of neuromuscular blockade, use of total intravenous anesthesia or a difference in median value of anesthetic gas of more than 0.2 measured between the patient being in the operation room and the patient being out of the operation room.
3. Period of data collection: between 01.01.2008 and 09.01.2016
4. Patient selection from institutions affiliated with the Multicenter Perioperative Outcomes Group (MPOG):
   a. University of Michigan Health System
   b. Oregon Health Sciences University
   c. University of Tennessee Medical Center
   d. University of Oklahoma Health Sciences Center
   e. Washington University School of Medicine
   f. University of Vermont
   g. Vanderbilt University
   h. University of Virginia Health System
   i. University Medical center Utrecht (the Netherlands)
   j. University of Colombia
   k. University of Pennsylvania.
5. We will only include the first intervention under general anesthesia during one particular hospitalization, to prevent patients with surgery related complications to become included.

Patient exclusion criteria

We defined several exclusion criteria to make our study as specific as possible, considering several factors that can influence the ETCO2 level:

1. Cardiac surgery: because of the influence of the pump-phase on the arterial and end-tidal carbon dioxide level. (Graham et al.; Song et al.)
2. Obstetric surgery: maternal physiological changes during pregnancy cause a decrease in arterial carbon dioxide content. (Templeton and Kelman; Tan and Tan)
3. Laryngeal mask airway: only patients receiving general anesthesia with use of an endotracheal tube will be included to ensure a reliable ETCO2 measurement.
4. ASA VI physical status
5. 1-lung ventilation
6. Cases with less than 20 valid ETCO2 and respiratory minute volume measurements.
7. Patients who received less than 40 minutes of general anesthesia between incision and the end of the surgical procedure, (or less than 50 minutes between induction end and end of the surgical procedure when incision is not available) will be excluded, since it might take some time before the end-tidal CO2 reaches the intended level and at the end of surgery the end-tidal CO2 level is often increased to establish spontaneous ventilation. This time-frame has been chosen based on expert consensus.
8. Patients receiving sodium bicarbonate, since that might increase the ETCO2. (Okamoto et al.)
9. Emergency cases
10. Patients who received 2 packed cells or more during surgery
11. Patients that received epinephrine to maintain their blood pressure
12. Use of vasopressin, milrinone, dobutamine, dopamine
13. Defibrillation and/or cardioversion
14. Ephedrine > 20mg
15. Phenylephrine > 400mcg/hr
16. Norephinephrine > 40mcg/hr

Criteria 9, 10 and 11 were added to the exclusion criteria since we believe that these patients might be in such a bad condition that the end-tidal CO2 can be either falsely low or, in neurosurgical emergency cases, is kept low on purpose.

We decided not to exclude patients who were breathing spontaneously, since we believe that an inacceptable increase (or decrease) in ETCO2 would lead to an intervention by the anesthesiologist. Since we aim to investigate which levels anesthesiologist find acceptable, we do not believe that a differentiation between controlled and spontaneous ventilation is of importance for our research question.

In addition, we will investigate the area under the curve data by site per year to determine if there are any outliers. Any site specific outliers will be removed from the analysis.

Data source

Perioperative data of the participating institutions are collected in the centralized MPOG database. This database contains the intraoperative anesthesia records that are documented in the anesthesia record keeping system within each institution. Also pre- and postoperative data are collected and can be derived from this database. (Freundlich and Kheterpal; Kheterpal) This database contains all, for this study, required data and no additional data sources will be used.

Data collection

The end-tidal CO2 and respiratory minute volume are measured continuously during general anesthesia by means of automated interfaces incorporated in the ventilator and gas analyzer. An average of these results is recorded every minute in the anesthesia record keeping system and stored in the centralized MPOG database. We will use the end-tidal CO2, measured by the automated interface in the expiratory part of the ventilation system. To establish the respiratory minute volume, we will either use the respiratory minute volume as measured by the ventilation system or we will calculate it, multiplying tidal volume with respiratory rate. For this calculation we will use the expired tidal volume and respiratory frequency measured in the expiratory limb of the breathing system. When these data are not available we will use the setting of the ventilator or the respiratory rate as measured by means of EKG bio impedance.

Outliers, defined as an ETCO2 measurement of less than 15 mmHg (2 kPa or 2%) or above 65 mmHg (8.6 kPa or 8.5%) will be excluded. For every patient, we will collect the total AUC for the ETCO2 groups (<28, 28-35, 35-45, > 45) and we will estimate the entire measurement time, to do a time-weight adjustment of the AUC. We will also establish the median overall ETCO2, which will be defined as the median of all valid ETCO2 measurements. We will only take into account the valid measurements from 10 minutes after incision (or 20 minutes after induction when applicable) until 10 minutes before procedure end, to allow the ETCO2 to reach the set level and to allow for the ETCO2 to increase at the end of surgery to establish spontaneous ventilation.

Respiratory minute ventilation is the product of tidal volume and respiratory rate. Outliers are defined as a tidal volume of less than 100ml or more than 1000 ml and/or a respiratory rate or less than 4 or above 25 or a minute volume of < 500ml/min or > 25000 ml/min. For every patient, we will establish the median overall minute volume ventilation, from all valid measurements from 10 minutes after incision (or 20 minutes after induction, when incision is not available) until 10 minutes before procedure end. We will do a separate analysis for the median minute volume ventilation measured between 10 and 15 minutes after incision (or between 20 and 25 minutes after induction as alternative) to investigate the primary ETCO2 level the anesthesiologist had in mind when initiating ventilation.

The total number of valid measurements of ETCO2 and minute volume ventilation will be recorded for every patient. Patients with less than 20 valid measurements will be excluded.
We will collect preoperative information relevant to our research question, including sex, height, weight, BMI and history of chronic obstructive pulmonary disease. These factors have been shown to be related to ventilator settings before. (Bender et al.) Data will be collected on ASA physical status as a marker of preoperative fitness of the patients. We will estimate whether it was a laparoscopic/robot assisted case or whether the case concerned intracranial or carotid surgery.

For every case, we will collect the primary anesthesia provider and the anesthesiologist. We will also estimate the blood pressure variability using the mean arterial blood pressure.

Statistical analysis

To investigate the primary outcome, we will use a random-effects quantile regression model with median ETCO2 as the dependent variable, time period as the independent variable, and institution as a random effect. We will then make a multivariable model adjusting for sex, height, BMI, age, ASA physical status and blood pressure variability as potential confounders. Four quantiles will be examined in these analyses based on the distribution of ETCO2: 0.10, 0.25, 0.75, and 0.90.

We will use the same modeling techniques to assess three of the previously mentioned subpopulations: laparoscopic surgery, patients with a history of COPD and intracranial surgery/carotid endarterectomy.

We will also estimate the median ETCO2 for every case an anesthesiologist supervised and group these data into three categories, based on who was the primary anesthesia provider (the anesthesiologist, the resident, or the Certified Registered Nurse Anesthetists), and institution and compare these values using a one-way ANOVA, as appropriate. By doing so we would like to estimate whether it is the supervising anesthesiologist or the primary anesthesia provider, determining the ETCO2 level.

For the secondary outcomes of median initial respiratory minute volume and median overall respiratory minute volume, we will perform separate multivariable quantile regressions as above, with the potential confounders listed as fixed effects and institution as a random effect. For the secondary outcome of TWA-AUC, ETCO2 will first be stratified into four groups: < 28, 28-35, 35-45 and > 45 mmHg. We will then estimate the area under the curve for each ETCO2 group and adjust for measurement time, resulting in a TWA-AUC for every group per case. The difference in TWA-AUC between groups will be assessed using a one-way ANOVA or Kruskal Wallis test, as appropriate. Finally, the difference in median ETCO2 levels between the start and end periods of the study will be examined using a two sample t-test or Mann-Whitney U test, as appropriate.

We will use descriptive statistics to describe the practice pattern derived from the questionnaires sent to the participating centers. When a similar pattern is found for several institutions, we will perform an Interrupted Time Series analysis for our primary outcome measure to estimate the change in trend before and after the intervention.

Management of missing data

We will exclude cases with less than 20 valid ETCO2 and/or minute ventilation measurements. When minute ventilation is not provided, we will calculate it from respiratory rate and/or tidal volume measurements. Again, cases with less than 20 valid measurements will be excluded.

For all of our subgroups we will do a complete case analysis.

Missing values in patient characteristics (age, sex, ASA classification, weight, height and BMI) will be handled using multiple imputation. We believe that we will be dealing with data that are "Missing at Random", which is mostly the case in epidemiologic research. Multiple imputation limits the amount of (selection) bias seen in other methods, such as complete case analysis. We therefore prefer to use multiple imputation and use all observed information to deal with selective missing values. (Donders et al.; Moons et al.). We will do an analysis with imputed data and one without the imputed data, by excluding patients with certain missing patient characteristics (namely, the possible confounders: BMI, height, weight, sex and ASA physical status) from the regression analysis but including them in the overall descriptive trend graphs, to estimate the effect of imputation on our data. We will report these results separately.

Several institutions did not contribute data during the entire study period from 01.01.2008 until 09.01.2016. We will provide insight by plotting the total number of patients included in our primary analysis over time in the plot showing the ETCO2 pattern over time.

Discussion Topics PCRC august 2016

1. Should we exclude spontaneous ventilation and how?
    a. *We decided to include spontaneous ventilation, assuming that the anesthesiologist will intervene when the ETCO2 becomes too low/high and most spontaneously breathing patients receive SIMV or Pressure Support, still regulated by the anesthesiologist.*
2. Start of data collection: How do we determine when ETCO2 is stable? Is it 10 minutes post intubation? Or potentially look at some level of variability to determine when the ETCO2 signal is stable?
    a. *Based on expert opinion: 10 minutes after incision, since the effect of induction and incision will then be attenuated.*
3. End of data collection: How do we determine when to stop ETCO2 data collection? Is it 10 minutes before the end of the operation? Or potentially look at some level of variability to determine when the ETCO2 signal is losing it's stability?
    a. *Again, based on expert opinion, 10 minutes prior to surgery end.*
4. Do we try to describe minute ventilation, or is ETCO2 the important component?
    a. *We will describe minute ventilation.*
5. What is the time frame for the study, since a lot of centers have spotty data
    a. *We will use 01.01.2008 until 09.01.2016 – we will plot the total number of patients included for every time period in the primary analysis plot*
6. Should we exclude laparoscopic cases in the primary analysis and include in the sensitivity analysis. Given the impact of insufflation on CO2 levels, we may simply be detecting a trend toward more laparoscopic cases?
    a. *We will exclude the subgroups from our primary analysis and use case description and CPT codes to define laparoscopic interventions*
7. Can we treat our confounders as a fixed effect or should we take into account that they can change over time as well?
    a. *We will look into the change over time of our possible confounders and based on the results, include them as either a fixed or a random effect in the model.*
8. Should we stratify between emergency and elective procedures?
    a. *Yes – emergency is excluded. Only elective cases will be studied.*
9. Remove the word target and phrase it as what are the practice patterns of ETCO2.
10. Because of the large sample size, is multiple imputation worth the time commitment?
    a. *For now, we think so.*
    b. *We will do a complete case analysis for our subgroups.*
11. How much change in practice patterns would you expect to see to have a clinically significant change in practice pattern?
    a. *10% relative change in clinical use would be clinically meaningful difference. This is added to the protocol*
12. Are you thinking of looking at outcomes such as death and ETCO2?

   a. *Yes, for Utrecht as a single center*
   b. *A multicenter study concerning postoperative wound infections might done in the future.*
13. Statistical analysis: we will use area under the curve and adjust for the time measured for each stratified groups. It will be time weighted.
   a. *Dr. Pace: It's simpler to use the median of all the values.*
      i. *But then, that makes an entire case into one value*
      ii. *We decided to use the TWA-AUC for four different ETCO2 ranges*
      iii. *We changed our analysis method: instead of a random effect linear regression model we use a quantile regression mode*
14. Procedures will be grouped in three month period. Why 3 months?
   a. *It's arbitrary*
   b. *We added into the protocol the first (2008) and last study period (2016) to see what changes*
15. Are you going to survey that the institution had a target and did something about the target?
   a. *Yes*
16. Do patients that received bicarb and epinephrine need to be excluded?
   a. *Yes*
   b. *Also excluded: ≥2 packed cells.*

Brief summary of additional changes after PCRC meeting

- *We will look into the influence of the primary anesthesia provider*
- *We will no longer look at the binary variable "hypocapnia yes or no"*
- *We will collect data on blood pressure variation*
- *We will only include the first intervention during an admission*
- *We do not look into ventilator mode, since ventilator mode is not well documented in the MPOG database*
- *Since we investigate four different ETCO2 stratification groups, we will use a 98.8% confidence interval to correct for multiple testing.*
- *When applicable, based on the survey results, we will perform an Interrupted Time Series analysis for our primary outcome measure.*

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