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BJAN-D-20-00198_Original Investigation

End-tidal carbon dioxide measurements as a surrogate to arterial carbon dioxide during pediatric laparoscopic surgeries: a prospective observational cohort study

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Abstract

Background: Maintaining normocapnia during mechanical ventilation in anesthetized children during laparoscopic surgeries is highly recommended. There is a debate regarding the use of capnography (ETCO₂) as a trend monitor for evaluation of arterial carbon dioxide levels (PaCO₂). We analyzed the relationship between ETCO₂ and PaCO₂ with time in elective pediatric laparoscopic surgeries.

Methods: This study was a prospective observational cohort analysis of 116 paired comparisons between PaCO₂ and ETCO₂ computed from 29 children (ASA I, 12–72 months). Arterial blood samples were withdrawn before, at 15 minutes and 30 minutes during pneumoperitoneum and 1 minute after deflation. ETCO₂ value was recorded simultaneously, while arterial blood was withdrawn. PaCO₂–ETCO₂ relationship was evaluated by Pearson's correlation coefficients and Bland Altman Method of agreement.

Results: Out of the 116 comparisons analyzed, a PaCO₂–ETCO₂ difference beyond 0 to ≤ 5 mmHg was recorded in 71 comparisons (61.2%) with negative difference in 34 comparisons (29.3%). A positive significant correlation between PaCO₂ and ETCO₂ was recorded before ($r = 0.617$, $p = 0.000$) and at

15 minutes ($r = 0.582$, $p = 0.001$), with no significant correlation at 30 minutes ($r = 0.142$, $p = 0.461$), either after deflation ($r = 0.108$, $p = 0.577$). Bland-Altman plots showed agreement between ETCO_2 and PaCO_2 before inflation with mean PaCO_2 - ETCO_2 difference 0.14 ± 5.6 mmHg (limits of 95% agreement -10.84 – 11.2 , simple linear regression testing p -value 0.971), with no agreement at 15 minutes (0.51 ± 7.15 , -13.5 – 14.5 , $p = 0.000$), 30 minutes. (2.62 ± 7.83 , -12.73 – 17.97 , $p = 0.000$), or after deflation (1.81 ± 6.56 , -10.93 – 14.55 , $p = 0.015$).

Conclusion: Usage of capnography as a trend monitor in pediatric laparoscopic surgeries may not be a reliable surrogate for PaCO_2 levels.

Trial registration: Clinical Trials. gov (Identifier: NCT03361657)

KEYWORDS

Children; Anesthesia; Laparoscopy; Mechanical ventilation; Arterial carbon dioxide; End tidal carbon dioxide

Introduction

In 2008 the World Federation of Societies of Anesthesiologists (WFSA) produced international standards for the safe practice in anesthesia which contained pulse oximetry and capnography.[1] Capnography provides a non-invasive estimation of arterial CO_2 levels. It permits physicians to titrate their protocols for mechanical ventilation to maintain normocapnia in operative theatres and in the intensive care.[2] To avoid perioperative central nervous system derangements, clinicians recommend the maintenance of normocapnia during intraoperative mechanical ventilation in pediatric patients specially in younger individuals, hemodynamic instability and in certain operative techniques such as carbon dioxide pneumoperitoneum in laparoscopic surgeries.[3-5]

Clinicians commonly evaluate the arterial carbon dioxide partial pressure by intermittent arterial blood gas analysis coupled with continuous recording of the end-tidal carbon dioxide by capnography.[6,7] Moreover, some clinicians aspirate a single arterial blood gas at the beginning of managing a case intraoperatively to calculate PaCO_2 - ETCO_2 difference then employ capnography as a trend monitor to evaluate and control changes in arterial carbon dioxide partial pressure value, afterwards.[8]

Normally, in healthy individuals there is a positive gap between arterial CO_2 and ETCO_2 ($\text{ETCO}_2 < \text{PaCO}_2$) of approximately 0.5 kPa (3.75 mmHg).[6] Negative gaps ($\text{ETCO}_2 > \text{PaCO}_2$) were

recorded in 34% of patients in pediatric critical care and during general anesthesia.[7,9,10] They occur most frequently in children aged 4–8 years,[9] with decreasing PaCO₂ values,[7,9] and with a dead space/tidal volume ratio of less than 0.4.[10] Certain procedures such as pediatric laparoscopic capnoperitoneum are associated with rapidly changing levels of both PaCO₂ and ETCO₂. [11] This in turn can further affect the PaCO₂–ETCO₂ difference.

In this study, our aim was to investigate the correlation and agreement between ETCO₂ measured by capnography and arterial PaCO₂ measured by arterial blood gas analysis and to calculate the PaCO₂–ETCO₂ difference during pediatric laparoscopic surgeries.

Patients and methods

Ethical considerations

This Prospective observational Cohort was conducted in the Pediatric hospital, faculty of medicine, Assiut University, Assiut, Egypt after obtaining an IRB approval from its Medical Ethics committee (Protocol ID: 17300081, date; 13-7-2017). Registration in Clinical Trials. gov (NCT03361657) was accomplished before patient enrollment. This study follows the “STROBE” guidelines for observational studies (STrengthening the Reporting of OBservational studies in Epidemiology). A written informed consent was taken from the legal guardians of children.

Study population

Twenty-nine children of both sexes, aged from 12 to 76 months, ASA I and II and scheduled for elective laparoscopic abdominal or urologic surgery (e.g undescended testis, repair for inguinal hernia, cholecystectomy), were enrolled in this study. Excluded from the study were patients with significant cardiac or respiratory disease.

Study protocol

No sedative premedication was administered. Monitoring included electrocardiography, non-invasive blood pressure, end-tidal capnography, and pulse oximeter (Shenzhen Mindray Bio-Medical Electronics Co, Ltd., China). Anesthesia induction started with sevoflurane inhalation followed with venous cannulation, and the administration of 1 µg.kg⁻¹ fentanyl, 1–1.5mg.kg⁻¹ lidocaine and atracurium 0.5 mg.kg⁻¹ for muscle relaxation. Older children also received iv propofol 2–3 mg.kg⁻¹ during induction

of anesthesia, if needed. An appropriately sized cuffed endotracheal tube was inserted. A cannula in the radial artery was inserted to be used for withdrawal of arterial blood samples. Patients were mechanically ventilated in volume-control mode using standard pediatric breathing circuits with tidal volume 8–10 mL.kg⁻¹, and at respiratory rates of 15–25 breaths per minute depending on the patient's age which finally adjusted to achieve an end- tidal CO₂ (ETCO₂) of 35–45 mm.Hg, and a target SaO₂% ≥ 97%. Any unnecessary connections that may increase the dead space were removed.

Laparoscopic surgeries were performed according to the standard protocols. Pneumoperitoneum was achieved using non- heated non- humidified CO₂ with the intra- abdominal pressure maintained at 10–12 mmHg. Sevoflurane in a 50% oxygen/air mixture and 0.15 mg.kg⁻¹ atracurium at fixed intervals were used for maintenance of anesthesia and muscle relaxation, respectively. All patients received 15 mg.kg⁻¹ intravenous paracetamol and 0.2 mg.kg⁻¹ dexamethasone.

Patients' hemodynamics, arterial blood gas analysis and ETCO₂ values were recorded at four predetermined time points: T1; after stabilization of the mechanical ventilation before inflation of pneumoperitoneum, T2; 15 min. after pneumoperitoneum, T3; 30 min. after pneumoperitoneum and T4; 1 min. after deflation of pneumoperitoneum before reversal of muscle paralysis and extubation.

ETCO₂ concentrations were measured using an adequately calibrated infrared mainstream capnometer (Datex Instrument Corp., Helsinki, Finland) with the Port connected between the proximal end of the endotracheal tube and the breathing circuit. Arterial blood samples were obtained coated with heparin. At each selected timepoint, the ETCO₂ value was recorded simultaneously while the arterial blood was withdrawn.

At the end of the surgery, sevoflurane was turned off and patients were extubated awake after reversal of muscle relaxation with neostigmine and atropine. After extubation, patients were transferred to the Post Anesthesia Care Unit (PACU) to be discharged to the ward, afterwards.

Statistics

The primary aim in this study was to investigate the relationship between ETCO₂ and PaCO₂ with time in pediatric laparoscopic surgery by computation of Pearson's correlation coefficient analysis and the agreement between the two monitors by the Bland Altman method. Secondary outcomes were the correlations and relationships between the PaCO₂–ETCO₂ difference and PaCO₂, ETCO₂, age, weight, and duration of the operative procedure. Using the G-Power calculator 3.1.9.7 for sample size determination, a minimum of 26 patients for this cohort would be sufficient for our statistical testing

based on a priori analysis with t tests family: correlation biserial model for one sample at a two tailed type I error of 0.05, and a power of 0.8 and effect size of 0.5. Thirty-two patients were enrolled to compensate for the dropouts.

Statistical analysis was conducted by the Statistical Package for the Social Sciences (SPSS) software version 20 for Microsoft Windows (SPSS Inc., Chicago, IL, USA). Data was checked for normality by visual inspection of histograms and by the Shapiro–Wilk test. Continuous data was presented as mean \pm SD with 95% confidence interval if normally distributed, and as median (Interquartile range and range) if not normally distributed. Categorical data was expressed as number and frequencies (%). Paired comparisons were analyzed using paired-t tests for normally distributed data and Wilcoxon signed rank test for abnormally distributed data. PaCO₂–ETCO₂ difference of 0 to \leq 5mmHg was considered as a clinically acceptable range. Correlation between variables was carried out by applying the Pearson correlation equation for linear relations and spearman correlation equation for non-linear correlation. The degree of correlation was determined based on the coefficient correlation (r) into perfect positive ($r = +1$), perfect negative ($r = -1$), no correlation ($r = 0$), high degree positive (r ranges from +0.75 to +1), high degree negative (r : -0.75 to -1), moderate degree positive (r : +0.25 to +0.75), moderate degree negative (r : -0.25 to -0.75), low degree positive (r : 0 to +0.25) and low degree negative (r : 0 to -0.25).

Bland-Altman plots at each studied time-point were used to investigate the agreement between ETCO₂ and PaCO₂ and this was furtherly confirmed by simple linear regression analysis.[12] A p -value of < 0.05 was the cutoff value for statistical significance.

Results

Thirty-two patients were enrolled in this study. Three patients were dropped because of protocol violation (diagnostic laparoscopy of short duration). Twenty-nine patients successfully completed the statistical analysis that yielded 116 paired comparisons between the PaCO₂ and the ETCO₂ at different timepoints. The patients' demographic and baseline characteristics are listed in Table 1.

Compared to the baseline value (T1), both the arterial carbon dioxide partial pressure (PaCO₂) and the end-tidal carbon dioxide (ETCO₂) significantly increased at 15 min. after inflation of the pneumoperitoneum and continued to increase at 30 min. after inflation ($p < 0.001$). After deflation of the pneumoperitoneum, both variables remained significantly higher than their respective base line values (p

< 0.001), (Table 2). The median PaCO₂-ETCO₂ difference increased at 30min. after inflation of the pneumoperitoneum and after deflation of the pneumoperitoneum ($p > 0.05$) (Table 2).

Out of the 116 paired comparisons of PaCO₂ and ETCO₂ analyzed in this cohort study, PaCO₂-ETCO₂ difference beyond 0 to ≤ 5 mmHg was recorded in 71 (61.2%) comparisons and negative PaCO₂-ETCO₂ difference was recorded in 34 comparisons (29.3%). One child showed a negative PaCO₂-ETCO₂ difference at the four timepoints studied. Negative PaCO₂-ETCO₂ difference was recorded at three timepoints in 4 children, at two timepoints in 4 children and at 1 timepoint in 10 children.

A moderate degree positive correlation between the PaCO₂ and ETCO₂ was recorded before inflation of the pneumoperitoneum ($r = 0.617$, $p = 0.000$) and at 15 min. after inflation of the pneumoperitoneum ($r = 0.582$, $p = 0.001$), (Fig. 1 A and B). No significant correlation was recorded between PaCO₂ and ETCO₂ at 30 min. after inflation of the pneumoperitoneum ($r = 0.142$, $p = 0.461$), either after deflation of the pneumoperitoneum ($r = 0.108$, $p = 0.577$). The PaCO₂, ETCO₂ and PaCO₂-ETCO₂ at the selected timepoints did not show significant correlation with age, weight, operative time, or Insufflation pressure (data not represented).

Bland-Altman plots showed an agreement between ETCO₂ and PaCO₂ before inflation of the pneumoperitoneum with mean of the PaCO₂-ETCO₂ difference as 0.14 ± 5.6 mmHg (limits of 95% agreement -10.84-11.2 with simple linear regression testing p -value as 0.971). No agreement between ETCO₂ and PaCO₂ was found at the other time points namely at 15 min. (mean difference 0.51 ± 7.15 , -13.5-14.5, $p = 0.000$), 30 min. (mean difference 2.62 ± 7.83 , -12.73-17.97, $p = 0.000$) either after deflation of the pneumoperitoneum (mean difference 1.81 ± 6.56 , -10.93-14.55, $p = 0.015$), (Fig. 2 A-D).

Discussion

Arterial blood gas analysis in this study revealed that PaCO₂ significantly increased after inflation of the pneumoperitoneum and remained high throughout the operation compared with baseline values. These findings are consistent with the findings recorded in similar studies.[11,13,14]

In a study on thirty adult patients (aged 42.87 ± 7.26 years) undergoing laparoscopic nephrectomy under general anesthesia a significant positive correlation between ETCO₂ and PaCO₂ was detected at baseline ($r = 0.772$, $p < 0.001$) and at 1h ($r = 0.880$, $p < 0.001$) and 2h ($r = 0.896$, $p < 0.001$) after pneumoperitoneum. The authors concluded that continuous ETCO₂ monitoring is a reliable indicator of the trend in arterial carbon dioxide fluctuations in ASA I-II patients undergoing laparoscopic nephrectomy under general anesthesia.[11] In contrast, we found a positive correlation

between PaCO₂ and ETCO₂ before inflation of the pneumoperitoneum ($r = 0.617$, $p = 0.000$) and at 15 min. after inflation of the pneumoperitoneum ($r = 0.582$, $p = 0.001$) with no correlation afterwards.

Ickx et al., investigated a cohort of 129 ASA I–II children (aged 1 day to 15 years old) intubated and mechanically ventilated undergoing different surgical procedures. Based on a single comparison between PaCO₂ and ETCO₂ performed prior to surgery, they reported a significant correlation between PaCO₂ and ETCO₂ ($r = 0.66$ and $p < 0.0001$). They also found a significant negative correlation between PaCO₂-ETCO₂ difference with age ($r = -0.42$, $p < 0.0001$) and weight ($r = -0.44$, $p < 0.0001$). They concluded that ETCO₂ remains a key tool as a trend monitor for arterial carbon dioxide, but PaCO₂ cannot be extrapolated accurately in children < 4 months or < 5 kg body weight.[9] In this study, age and weight did not show correlation with changes in the PaCO₂, ETCO₂ either with the PaCO₂-ETCO₂ difference. An explanation to our findings is that we investigated a homogenous sample with narrow age range (12–72 months) compared with the Ickx's study.[9]

Onodi et al. conducted a retrospective analysis on 799 pediatric patients scheduled for different surgical operations who were intubated and mechanically ventilated (median age 6.8 [range: 0–18.1] years old). Data sets from 2452 blood gas analysis samples were coupled with vital signs monitoring, anesthesia gas analysis and spirometry data. They found that the bias in mean arterial to end-tidal carbon dioxide difference was -0.18 kPa (limits of 95% agreement -1.10 to 0.74) and 71.2% of samples demonstrated negative values. They concluded that ETCO₂ monitoring can be considerably misleading particularly in healthy patients undergoing surgery.[15] In accordance, Yang et al. in their prospective cohort study that included 445 paired comparisons of PaCO₂ and ETCO₂ from 137 pediatric patients with traumatic brain injury who were intubated and mechanically ventilated in PICU, they also found a weak agreement between PaCO₂ and ETCO₂. They concluded that ETCO₂ values are not a reliable substitute for PaCO₂ values during the first 24 hours after pediatric traumatic brain injury.[16] In accordance, in this study, agreement between the two monitors was recorded only before inflation of the pneumoperitoneum, with no agreement either during or after deflation of the pneumoperitoneum. These findings suggest that ETCO₂ monitoring during laparoscopic surgery may not be accurate specially in prolonged cases.[17,18]

Nunn and Hill recommended that the arterial to end-tidal CO₂ difference (PaCO₂-ETCO₂) during anesthesia in healthy individuals is relatively constant assuming that the gap between PaCO₂ and ETCO₂ is positive (PaCO₂ $>$ ETCO₂) and of approximately 0.5 kPa that increases with age.[6] In contrast, in this study the PaCO₂-ETCO₂ difference showed variations between patients and in the same patient at

different timepoints. These results also suggest that ETCO₂ monitoring can be misleading in the patient group we investigated.

Anatomic and physiologic dead space results in PaCO₂ values that are higher than ETCO₂ values when paired comparisons are done simultaneously.[16] The alveolar CO₂ concentrations are a little higher than the arterial CO₂ concentrations in blood. This positive gap is attributed to the mixture between alveolar gas that contains CO₂ and the exhalation gas deprived from CO₂ coming from the anatomic dead space.[16,19] However, in this study 29.3% of our PaCO₂–ETCO₂ paired comparisons showed negative gaps with ETCO₂ > PaCO₂. Similar studies also reported this negative gap in healthy anesthetized children of 71.3% [15] and 34%,[9] and in pediatric intensive care (22.7%).[7]

A negative PaCO₂–ETCO₂ difference has been reported in children aged 4–8 years,[9] with decreasing PaCO₂ values[7,9] and with a dead space/tidal volume ratio of less than 0.4.[10] The normal physiologic dead space to tidal volume ratio (V_d/V_t) is 0.20–0.35.[10,19,20] Physiologic dead space ventilation is the sum of anatomical dead space from the conducting airways and alveolar dead space due to disease processes and/or ventilatory techniques. Increase in physiologic dead space increases the PaCO₂–ETCO₂ difference.[10,19,20]

Pneumoperitoneum with carbon dioxide as an insufflating gas is associated with CO₂ absorption and increased CO₂ concentration in the bloodstream, increasing both ETCO₂ and PaCO₂ values.[21] Ventilatory techniques commonly used to overcome such problem (higher respiratory rates and low tidal volumes) can iatrogenically increase the physiologic dead space with inadequate ventilation of dependent well perfused alveoli.[7] This results in the accumulation of CO₂ in the lower airway thus the exhaled CO₂ in the terminal part of phase-3 capnography may exceed the mean PaCO₂, resulting in a negative PaCO₂–ETCO₂ difference.[7,9] Onodi et al. in their study found that hypocapnia is a strong predictor for lower or more negative PaCO₂–ETCO₂ difference.[15] So, as a trial to control elevations of PaCO₂ in pediatric laparoscopy, iatrogenic hypocapnia can pass unnoticed with its deleterious effects on the cerebral circulation in this vulnerable age group.

Non-invasive transcutaneous carbon dioxide (PtcCO₂) monitoring is another modality that can continuously predict PaCO₂ particularly in prolonged laparoscopic procedures and the agreement between PtcCO₂ and PaCO₂ has been confirmed in many studies.[18,22-24] Future studies are needed to prove its' agreement with the PaCO₂ in children and to investigate how to overcome its technical drawbacks such as slow response time, long warm-up time and difficulties with patients' skin contact.

In this study, arterial blood gas samples were withdrawn through an arterial cannula inserted in the radial artery to avoid repeated arterial punctures. The overall incidence of complications of arterial cannulation in infants and children is less than 0.2%. We selected the radial artery for cannulation because, it carries less risk of complications compared to other routes such as the femoral route.[25]

Limitations to this cohort were that we investigated patients with healthy lungs anesthetized in the supine position and the small sample size. Further studies of larger sample size investigating diverse pediatric populations undergoing laparoscopic surgeries under different positions are needed.

In conclusion, we recommend that the use of capnography as a trend monitor during pediatric laparoscopic surgeries may not be a reliable surrogate for arterial PaCO₂ levels.

Financial support

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Question

Is the relationship between capnography (ETCO₂) and arterial carbon dioxide levels (PaCO₂) is constant so that we can rely on ETCO₂ as a reliable surrogate to PaCO₂ in pediatric laparoscopy?

Meaning

The use of capnography in pediatric laparoscopic surgeries may not be a reliable surrogate for arterial PaCO₂ levels.

Findings

Out of the 116 paired comparisons of PaCO₂ and ETCO₂ analyzed in this cohort study a PaCO₂–ETCO₂ difference beyond the recommended range of 0 to ≤ 5 mmHg was recorded in 71 (61.2%) comparisons with Negative difference (ETCO₂ > PaCO₂) in 34 comparisons (29.3%). A positive correlation between PaCO₂ and ETCO₂ was recorded before and at 15 min. after inflation of pneumoperitoneum with no correlation afterwards. Bland Altman method showed agreement between ETCO₂ and PaCO₂ before inflation of the pneumoperitoneum, with no agreement during or after deflation of the pneumoperitoneum.

Conflicts of interest

The authors declare no conflicts of interest.

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Figure 1 A, Relationship between the End-Tidal Carbon Dioxide (ETCO₂) and Arterial Carbon Dioxide (PaCO₂) before inflation of the pneumoperitoneum processed by Pearson correlation coefficient. Correlation is significant at the 0.01 level (2-tailed). **B**, Relationship between the End-Tidal Carbon Dioxide (ETCO₂) and Arterial Carbon Dioxide (PaCO₂) at 15 min. after inflation of the pneumoperitoneum processed by Pearson correlation coefficient. Correlation is significant at the 0.01 level (2-tailed).

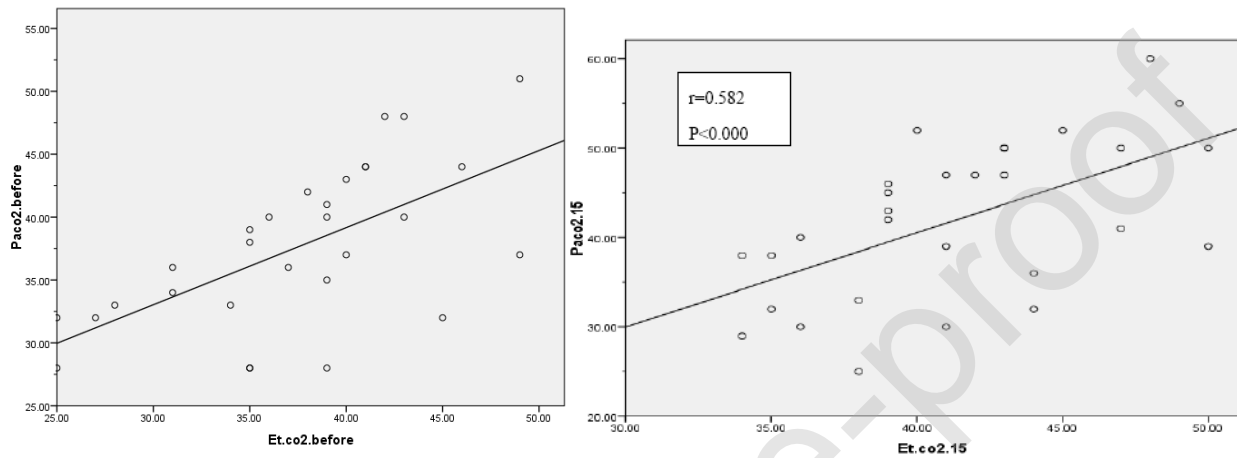


Figure 2 A, Bland-Altman plots comparing PaCO₂ and ETCO₂ before inflation of the pneumoperitoneum. Mean difference is 0.14 ± 5.6 mmHg (limits of 95% agreement -10.84–11.2 mmHg). Mean1; Each PaCO₂–ETCO₂ Pair Mean (mmHg) before inflation of the pneumoperitoneum. Diff1; Difference in PaCO₂–ETCO₂ Pair (mmHg) before inflation of the pneumoperitoneum, (n = 29). B, Bland-Altman plots comparing PaCO₂ and ETCO₂ at 15 min. after inflation of the pneumoperitoneum. Mean difference 0.51 ± 7.15 (limits of 95% agreement -13.5–14.5). Mean2; Each PaCO₂–ETCO₂ Pair, Mean (mmHg) at 15 min. after inflation of the pneumoperitoneum. Diff2; Difference in PaCO₂–ETCO₂ Pair (mmHg) at 15 min. after inflation of the pneumoperitoneum, (n = 29). C, Bland-Altman plots comparing PaCO₂ and ETCO₂ at 30 min. after inflation of the pneumoperitoneum. Mean difference 2.62 ± 7.83 (limits of 95% agreement -12.73–17.97) Mean3; Each PaCO₂–ETCO₂ Pair, Mean (mmHg) at 30 min. after inflation of the pneumoperitoneum. Diff3; Difference in PaCO₂–ETCO₂ Pair (mmHg) at 30 min. after inflation of the pneumoperitoneum, (n = 29). D, Bland-Altman plots comparing PaCO₂ and ETCO₂ after deflation of the pneumoperitoneum. Mean difference 1.81 ± 6.56 (limits of 95% agreement -10.93–14.55) Mean4; Each PaCO₂–ETCO₂ Pair, Mean (mmHg) after deflation of the pneumoperitoneum. Diff4; Difference in PaCO₂–ETCO₂ Pair (mmHg) after deflation of the pneumoperitoneum, (n = 29).

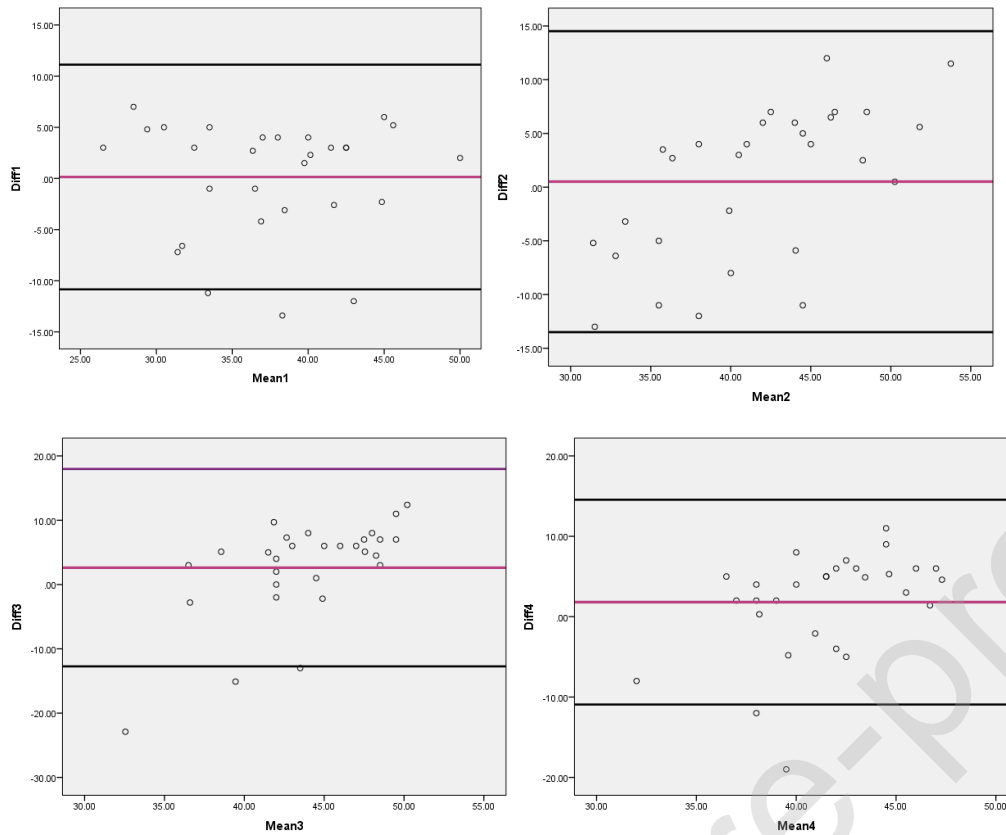


Table 1 Patients' demographic and clinical characteristics.

Item	Study cohort (n = 29)
Age (months)	36 (12–72)
Weight (Kg)	15 (8–35)
Sex: Male/female	24/5
ASA Class: I/II	29/0
Insufflation pressure (cm.H ₂ O)	12 (10–12)
Operation time (min.)	39.7±14.1 (34.3–45.1)
Pathological diagnosis:	
Chronic cholecystitis	4
Congenital Inguinal hernia	4
Congenital adrenal hyperplasia	2
Gastric volvulus	1
Undescended testis	18

Data presented as median (range), mean (\pm SD) with 95% confidence interval, range, and number.

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Table 2 Paired sample statistics of Arterial Carbon Dioxide Partial pressure (PaCO₂) and the End-Tidal Carbon Dioxide (ETCO₂) (mmHg).

Study cohort (n = 29) Time	Arterial carbon dioxide partial pressure (PaCO ₂)	End-tidal carbon dioxide (ETCO ₂)	Arterial-end-tidal carbon dioxide difference (PaCO ₂ -ETCO ₂)
T1: Before inflation	37.6±6.3 (35.2–40.0)	37.5±6.4 (35.04–39.9)	2.7 (6.9) (-13.0–7.0)
T2: 15 min. after inflation	42.0±8.8 ^b (38.6–45.2)	41.4±4.8 ^c (39.6–43.2)	3.0 (11.6 t) (-13–12.0)
T3: 30 min. after inflation	45.2±7.5 ^c (42.4–48.1)	42.6±3.6 ^c (41.2–43.9)	5.1 (6.5) (-22.9–12.4)
T4: After deflation	42.3±5.9 ^b (40.1–44.6)	40.5±3.6 ^c (39.1–41.9)	4.0 (6.9) (-19.0–11.0)

Data presented as mean ± SD with 95% confidence interval and median (Interquartile Range [IQR] and range). $p < 0.05$ denotes significant difference compared to baseline value (T1).

^a $p < 0.05$.

^b $p < 0.01$

^c $p < 0.001$.