

Mainstream Capnography Correlates Well with Central Venous Carbon Dioxide Levels in Non-intubated Children in PACU

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ABSTRACT

Introduction: Monitoring exhaled Carbon Dioxide (CO₂) in non-intubated patients is challenging but has value for detecting hypoventilation, apnoea and hypercarbia. The study investigated a mainstream mask capnography system (cap-ONE[®]) especially designed for children.

Aim: To compare the accuracy of peak exhaled CO₂ (PexCO₂) using mainstream mask capnography to partial pressure of central venous CO₂ (PcvCO₂).

Materials and Methods: After Institutional Review Board approval, this prospective study was conducted enrolling children (weight range 7–40 kg) undergoing minor procedures who had indwelling central venous access for clinical indications. Infant and paediatric mainstream capnography masks were used according to patient body weight. Central venous blood was collected for analysis of PcvCO₂ during capnography recording.

Values for PcvCO₂ and PexCO₂ obtained from mainstream mask capnography monitoring were compared in individual patients.

Results: Forty children were enrolled and analysed. All patients had an uneventful anaesthetic course and entered the PACU without respiratory compromise. The average and Standard Deviation (SD) of PcvCO₂ were 47.5 (5.0) mmHg. Measurement error between PexCO₂ at blood sampling was 6.1 (SD; 3.2) mmHg. When PcvCO₂ >50 mmHg and PexCO₂ >45 mmHg from the mask was used as the threshold for hypercapnia the sensitivity was 77%, specificity 96%, and Area Under the Curve (AUC) 0.866 at the time of blood sampling.

Conclusion: Measurement error between PexCO₂ and PcvCO₂ was similar to known exhaled-arterial PCO₂ difference (4–6 mmHg). We conclude that a mainstream mask capnography is a reliable method to assess hypoventilation and hypercapnia in non-intubated children.

Keywords: Blood gas analysis, Paediatric, Respiratory function tests

INTRODUCTION

Capnography is widely used in anaesthesia and critical care medicine, typically for monitoring patients with an endotracheal tube or Laryngeal Mask Airway (LMA) [1–5]. Capnography has also been used for non-intubated patients to detect apnoea or respiratory insufficiency [6,7].

Side-stream capnography systems aspirate exhaled gas and measure CO₂ remote from the patient. In non-intubated children for cardiac catheterisation, side-stream capnography demonstrated good correlation between exhaled CO₂ and arterial, central venous and capillary PCO₂ [8]. However, stable monitoring of CO₂ using a conventional side stream system can be challenging. The CO₂ sampling tube is prone to obstruction from moisture and high flow oxygen administration either via oxygen mask or nasal cannula will alter the CO₂ readings. Mainstream capnography systems measure CO₂ at the site of exhaled gas and may be less affected by administered oxygen as compared to side-stream systems. A novel mainstream capnography system (cap-ONE[®] and cap-ONE[®] mask) was recently developed by Nihon Kohden Corporation, Tokyo, Japan and its accuracy has been reported in adult and mannequin model studies [9–11].

We have previously showed that peak exhaled CO₂ (PexCO₂) measurements, in non-intubated children were normally distributed with a smaller variance as compared to side-stream capnography [12]. This remained true regardless of oxygen flow rate or whether patients were mouth breathing. In addition to less variability in measurement it is hoped that mainstream capnography provides PexCO₂ that correlates with CO₂ measurements from blood.

Our hypothesis is that PexCO₂ measurements from a mainstream capnography system (cap-ONE[®]) will correlate with central venous PCO₂ and can be used for detecting hypercapnia in non-intubated

children. Our primary outcome will be the agreement between PexCO₂ at different time points and PvCO₂ from central venous blood sampling. Secondary analyses will explore the patient characteristics (gender, and mask size) that may affect the measurement error as well as the performance of the cap-ONE mask for discriminating hypercapnia.

MATERIALS AND METHODS

This prospective study was approved by the Children's Hospital Los Angeles Institutional Review Board (IRB; CHLA-15-00035). Independent observers for the study (a research nurse and a research respiratory therapist) were trained in capnography by a senior staff anaesthesiologist and company technical consultant. This study was conducted from March 2015 to January 2017 and adheres to STROBE guidelines.

Selection of Participants

All the participants were recruited from outpatient surgery centre at Children's Hospital Los Angeles. Inclusion criteria were ASA physical status classification 1–3 patients with a body weight of 7 to 40 kg undergoing minor procedures with pre-existing or intraoperative placed central venous access. Exclusion criteria included abnormal facial anatomy which may be unfit to the cap-ONE[®] mask, the presence of major cardiac anomalies causing intracardiac shunt, cardiopulmonary/neurological instability anticipated to cause acute changes in respiratory status, baseline SpO₂ <88%, and/or, baseline respiratory rate less than 15 or more than 60 breaths per minute. Demographic information was collected for eligible participants. Written, informed consent was obtained on the day of procedure.

Children less than 20 kg body weight wore infant cap-ONE[®] mask (small mask), whereas children more than 20 kg wore paediatric cap-ONE[®] mask (medium mask) according to the manufacturer's instructions.

Data Sampling

The recording of capnography waveforms was started at PACU entry and continued for five minutes. The initial O₂ flow rate was 2 L/minute. We recorded SpO₂, RR, consciousness status (awake, drowsy, or asleep), existence of an airway support device (oral airway, nasal airway); the duration the patient wore the O₂ mask, and the duration of PACU stay. All additional monitoring was performed with the BSM-6301A monitoring system (Nihon Kohden, SpO₂ probe, MASIMO). Central venous blood samples were collected once during the time the capnography waveforms were being recorded and were tested for partial Pressure of Carbon Dioxide (PcvCO₂) using the Epop blood gas and electrolyte analysis system (Alere, Waltham, MA). To blind the investigators, separate research assistants measured mean peak expiratory CO₂ and PcvCO₂. Further, blood gas measurements were obtained in a separate location.

STATISTICAL ANALYSIS

Sample size of 40 was calculated with linear regression testing for patient factors that had an association with the measurement error at each time point, was sufficient to detect significance with 95% power. Primary analysis included assessment of agreement between peak value of exhaled CO₂ (PexCO₂) and central venous CO₂ (PvCO₂). Secondary analysis included assessment of the patient and mask characteristics that affect the measurement error at each time point as well as the performance of the cap-ONE® mask for discriminating hypercapnia. Measurement error was assessed at four time points; at the time of PvCO₂ blood sampling, 0-10 seconds, 10-20 seconds, and 20-30 seconds to identify if there was a lag in PexCO₂ measurements. Eight patient characteristics and one mask characteristic were assessed for association with measurement error defined as the difference in mmHg between the PexCO₂ and the PvCO₂. Hypercapnia defined as PvCO₂ >50 mmHg was used as the gold standard while >45 mmHg was used as the threshold for hypercapnia using PexCO₂ from the mask. Patient characteristics such as BMI, age, gender, and temperature were collected at pre-op while heart rate, respiratory rate, and mask size were collected at the time of PACU arrival. The relative percent change in mean arterial pressure was defined as $\frac{MAP_{preOp} - MAP_{PACU}}{MAP_{preOp}} \times 100$ and was further dichotomised into >20% change or ≤20% change. Status of pre-existing conditions that might affect respiration was defined by the lead investigator based upon pre-op diagnosis and procedure performed.

Agreement between PexCO₂ and PvCO₂ at each time point was assessed visually using Bland-Altman plots and summary statistics describing measurement error. Univariate analysis using generalised linear modelling was used to assess each patient characteristic separately at each time point at the 0.10 significance level to determine if there was an effect on measurement error. Sensitivity, specificity, and Area Under the Curve (AUC) were used to assess the performance of the cap-ONE mask in identifying hypercapnia. All statistical analysis was performed with SAS Version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

Forty children were enrolled and analysed. All patients had an uneventful anaesthetic course and entered the PACU without respiratory compromise. Study demographics are shown in [Table/Fig-1]. Seventeen children wore small mask (age range 21-65-month-old, mean 47.7, SD 15.4; weight range 11-20 kg, mean 16, SD 2.5). Twenty-three children wore medium mask (age range 41-144 months, mean 79.8, SD 25; weight range 9-37 kg, 22.8, SD 6.2). One patient had a nasal airway in place to support airway patency at the time of capnography. Distributions of PcvCO₂ were denied non-normality (p=0.81, 0.52, respectively) by skewness/kurtosis test.

Agreement between PvCO₂ and Mask PexCO₂ [Table/Fig-2a-d]: Similar differences in PvCO₂-PexCO₂ were found at each time point: At sampling (6.1±3.2 mmHg), 0-10 seconds (6.08±2.1 mmHg), 10-

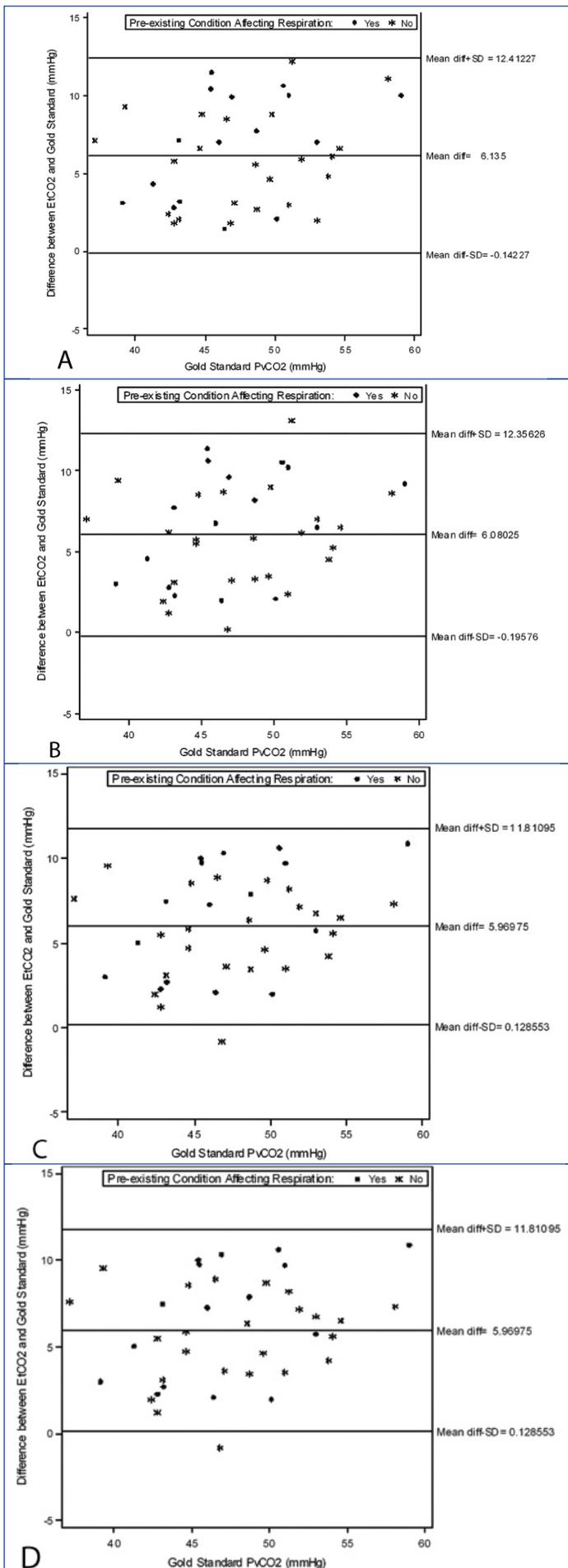
Variables	All	
	N=40	
Gender		
Male	N (%)	21 (52.50%)
Female	N (%)	19 (47.50%)
Age, months	Mean±sd	65.53±26.3±
	Median (Q1, Q3)	62.50 (49.0, 77.5)
Pre-existing Condition Affecting Respiration:		
No	N (%)	24 (60.00%)
Yes	N (%)	16 (40.00%)
Temperature (°C), at Pre-Op	Mean±sd	36.35±0.2
	Median (Q1, Q3)	36.40 (36.2, 36.5)
BMI, at Pre-op	Mean±sd	16.24±2.7
	Median (Q1, Q3)	16.09 (15.1, 17.0)
Cap-ONE Mask Size		
Small (infant)	N (%)	17 (42.50%)
Medium (paediatric)	N (%)	23 (57.50%)
Relative Percent Change in Mean Arterial Pressure		
≤20%	N (%)	26 (65.00%)
>20%	N (%)	14 (35.00%)
Heart Rate (bpm), at PACU arrival	Mean±sd	92.25±14.8
	Median (Q1, Q3)	92.50 (85.0, 98.0)
Respiratory Rate (breaths/min), at PACU arrival	Mean±sd	21.33±4.0
	Median (Q1, Q3)	21.00 (19.0, 23.0)
PcvCO ₂ , mmHg	Mean±sd	47.46±5.0
	Median (Q1, Q3)	46.85 (43.1, 51.0)
Measurement Error at Time of Blood Sample, mmHg	Mean±sd	6.14±3.2
	Median (Q1, Q3)	6.35
Measurement Error at 0-10 seconds, mmHg	Mean±sd	6.08±2.1
	Median (Q1, Q3)	6.17 (3.1, 8.6)
Measurement Error at 10-20 seconds, mmHg	Mean±sd	5.97±2.9
	Median (Q1, Q3)	6.10 (3.4, 8.3)
Measurement Error at 20-30 seconds, mmHg	Mean±sd	5.88±2.9
	Median (Q1, Q3)	5.88 (3.6, 8.4)

[Table/Fig-1]: Summary statistics by demographics and pre-existing condition.

20 second (5.9±2.9 mmHg), 20-30 seconds (5.9±2.9 mmHg). Each time point displayed a larger PvCO₂ mmHg than PexCO₂ mmHg, on average. Bland Altman plots revealed points outside of the Limits of Agreement at the 0-10, 10-20, and 20-30 second time points while at the time of blood collection all points were within the limits of agreement. Across all time points, larger bias was seen at higher levels of PvCO₂ (>55 mmHg). When identifying those with pre-existing conditions affecting respiration, the summary statistics revealed that those without had smaller measurement error at 20-30 seconds, although this was not statistically significant (p=0.18).

Factors that showed evidence of association (p<0.10) with measurement error from the univariate analyses at each time point are displayed in [Table/Fig-3,4]. Gender showed that there was a trend towards females having lower measurement error, on average. For females, the mean difference was 1.9 mmHg lower at the time of blood sampling (p=0.058), 1.7 mmHg lower at 0-10 seconds (p=0.094), and 1.7 mmHg lower at 20-30 seconds (p=0.071). BMI was a significant factor for predicting measurement error at 20-30 seconds (p=0.035) shown in [Table/Fig-4]. For every one unit increase in BMI, there is an average decrease in the measurement error of 0.37 mmHg, suggesting that patients with higher BMI have a closer PvCO₂ and PexCO₂ measured by CapOne® mask [Table/Fig-5].

Sensitivity/Specificity Analysis in Testing for Hypercapnia: Based on PvCO₂ levels obtained from the blood draw, 13 out of the 40 patients



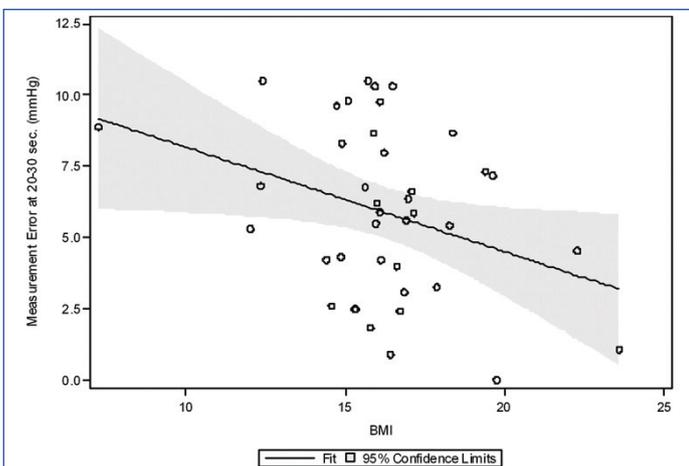
[Table/Fig-2]: Bland-Altman analyses of PcvCO₂ and PexCO₂ at the time of blood sampling (A), 0-10 seconds after blood sampling (B), 10-20 seconds after blood sampling (C), and 20-30 seconds after blood sampling (D). The mean differences (bias) between PcvCO₂ and PexCO₂ were: (A) 6.1 mmHg±3.2 mmHg, (B) 6.1 mmHg±3.2 mmHg, (C) 6.0 mmHg±2.9 mmHg, (D) 5.9 mmHg with SD of 2.9 mmHg.

Measurement Error at the time of blood sampling			
Characteristic Tested	Model Estimate	95% C.I.	p-value
Gender (Female vs. Male)	-1.91	(-3.89, 0.07)	0.058
Age (months)	0.005	(-0.04, 0.04)	0.81
Pre-existing condition affecting respiration (Yes vs. No)	1.04	(-1.06, 3.13)	0.32
Pre-Op Temperature	3.14	(-1.41, 7.69)	0.17
BMI	-0.21	(-0.59, 0.17)	0.28
Mask Size (Medium vs. Small)	0.09	(-2.01, 2.19)	0.93
Relative percent change in Mean Arterial Pressure (>20% vs. ≤ 20%)	-0.03	(-2.21, 2.15)	0.98
Heart Rate at PACU arrival	0.0002	(-0.07, 0.07)	>0.99
Respiratory Rate at PACU arrival	0.10	(-0.16, 0.36)	0.43
Measurement Error at 0-10 seconds			
Gender (Female vs. Male)	-1.70	(-3.70, 0.30)	0.09
Age (months)	0.004	(-0.04, 0.04)	0.84
Pre-existing condition affecting respiration (Yes vs. No)	1.06	(-1.03, 3.15)	0.31
Pre-Op Temperature	2.88	(-1.69, 7.45)	0.21
BMI	-0.22	(-0.60, 0.16)	0.26
Mask Size (Medium vs. Small)	-0.13	(-2.23, 1.97)	0.90
Relative percent change in Mean Arterial Pressure (>20% vs. ≤ 20%)	0.24	(-1.93, 2.42)	0.82
Heart Rate at PACU arrival	0.004	(-0.07, 0.07)	0.91
Respiratory Rate at PACU arrival	0.08	(-0.18, 0.34)	0.55
Measurement Error at 10-20 seconds			
Gender (Female vs. Male)	-1.40	(-3.28, 0.48)	0.14
Age (months)	0.01	(-0.03, 0.05)	0.54
Pre-existing condition affecting respiration (Yes vs. No)	1.17	(-0.77, 3.10)	0.23
Pre-Op Temperature	3.28	(-0.93, 7.49)	0.12
BMI	-0.27	(-0.63, 0.08)	0.12
Mask Size (Medium vs. Small)	0.35	(-1.60, 2.31)	0.72
Relative percent change in Mean Arterial Pressure (>20% vs. ≤ 20%)	0.11	(-1.91, 2.14)	0.91
Heart Rate at PACU arrival	0.01	(-0.06, 0.07)	0.78
Respiratory Rate at PACU arrival	0.04	(-0.20, 0.28)	0.73
Measurement Error at 20-30 seconds			
Gender (Female vs. Male)	-1.68	(-3.52, 0.15)	0.071
Age (months)	0.01	(-0.03, 0.05)	0.59
Pre-existing condition affecting respiration (Yes vs. No)	1.31	(-0.60, 3.22)	0.17
Pre-Op Temperature	2.67	(-1.55, 6.88)	0.21
BMI	-0.37	(-0.71, -0.03)	0.035
Mask Size (Medium vs. Small)	0.28	(-1.66, 2.22)	0.77
Relative percent change in Mean Arterial Pressure (>20% vs. ≤ 20%)	-0.12	(-2.13, 1.89)	0.90
Heart Rate at PACU arrival	0.02	(-0.05, 0.08)	0.62
Respiratory Rate at PACU arrival	0.07	(-0.16, 0.31)	0.53

[Table/Fig-3]: Univariate results for characteristics affecting measurement error from time of sampling to 10 seconds, 10-20 seconds, 20-30 seconds.

had CO₂ levels above 50 and were assumed to have hypercapnia. Using 45 as a threshold for PexCO₂ levels, we conducted sensitivity and specificity tests to determine how well the mask can detect hypercapnia at different times.

Discrimination of hypercapnia at each time point is summarised in [Table/Fig-6]. Measurements are: at sampling (sensitivity 77%, specificity 96%), 0-10 seconds (sensitivity 77%, specificity 89%), 10-20 seconds (sensitivity 69%, specificity 93%), and 20-30 seconds (sensitivity 77%, specificity 89%).



[Table/Fig-4]: Predicted Measurement Error at 20-30 seconds after blood sampling by BMI. BMI was a significant factor for predicting measurement error at 20-30 seconds (p=0.035). For every one unit increase in BMI, there is an average decrease in the measurement error of 0.37 mmHg.

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[Table/Fig-5]: Univariate results for characteristics affecting measurement error from time of 10-30 seconds.

Time Point	Sensitivity	Specificity	AUC
At the time of blood sampling	77%	96%	0.866
0-10 seconds	77%	89%	0.829
10-20 seconds	69%	93%	0.809
20-30 seconds	77%	89%	0.829

[Table/Fig-6]: Exhaled CO₂ discrimination of hypercapnia at each time point. *True hypercapnia was defined at PcvCO₂>50 mmHg while the mask threshold (PexCO₂) was >45 mmHg.

The AUC was 0.866 at blood draw, 0.829 at 0-10 seconds, 0.809 at 10-20 seconds, and 0.829 at 20-30 seconds. This suggests the PexCO₂ measurement taken at blood draw was the most accurate in testing for hypercapnia. However, it is worth mentioning that three patients had EtCO₂ levels of exactly 45 at that point, which barely identified them as true negatives and significantly increased the AUC at that point.

DISCUSSION

We found that peak exhaled CO₂ (PexCO₂) measured by mainstream mask capnography system (cap-ONE®) correlated well with PvCO₂ measured with a central venous blood gas (PcvCO₂). Univariate analyses showed that BMI was the only significant factor for predicting measurement error between PcvCO₂ and PexCO₂. When PcvCO₂ >50 mmHg and PexCO₂ >45 mmHg from the mask was used as the threshold for hypercapnia, sensitivity, specificity, and AUC indicated good reliability of this device detecting hypercarbia. We believe that the mainstream mask capnography device could be used to monitor for hypoventilation and hypercarbia in children recovering from anaesthesia.

In our previous study, we compared the precision of mainstream mask (cap-ONE®) capnography and side-stream nasal cannula capnography in non-intubated children in a PACU setting [12]. Measurement of PexCO₂ values by mainstream mask system showed a normal distribution with a smaller SD and was less affected by O₂ flow change than side stream sampling in predictable fashion. The difference in average CO₂ values between O₂ flow rates of 0.25 L/minute and 2 L/minute was 0.8 mmHg whereas the difference in average CO₂ between O₂ flow rates of 0.25 L/minute and 5 L/minute was 2.0 mmHg. We used this prior information to choose 2 L/minute as the flow rate for this study. We chose to compare PexCO₂ to blood gas values drawn from a central venous line (PcvCO₂). Normally, when the PCO₂ is measured invasively, there is a slight discrepancy between blood values and exhaled CO₂ due to dead space of the lung and bronchial tree regardless of intubated or non-intubated patients. Neonates and infants were reported to smaller blood-exhaled PCO₂ differences than older counterparts [13]. Arterial blood gas measurement of carbon dioxide (PaCO₂) is considered the gold standard. However, collecting arterial blood samples in non-anesthetised children in PACU is technically challenging. In adults, several authors have compared PaCO₂ to PvCO₂ drawn centrally and/or from peripheral venous blood [14-16]. In general, PCO₂ of central venous blood and peripheral venous blood correlated well to arterial PCO₂. Arterial PCO₂ is consistently lower than central venous and peripheral venous PCO₂ as expected since CO₂ is transported from pulmonary arterial blood to alveoli [8,14-17]. The differences between central venous PCO₂ and arterial PCO₂ are consistently smaller than those between arterial and peripheral venous PCO₂ [8,16,17]. Given

this information and ease of use we chose central venous blood as a standard of PCO_2 measurement in examining accuracy of peak exhaled CO_2 measurement by the mainstream mask system.

When capnography is used to evaluate the end-tidal concentration of CO_2 , it must be interpreted in conjunction with other clinical findings such as the work of breathing, CO_2 transport and elimination as well as changes in cardiac output. In non-intubated adult patients, a mainstream compared with a side-stream capnography system better reflected arterial PCO_2 measurements. Although the patient population was healthy, capnometry may not correctly identify hypercarbia in the presence of lung disease (e.g., high V/Q mismatch) or small tidal volumes, factors commonly found in sicker patients [9]. In our study, we examined children without any acute respiratory compromise after short minor surgical procedures. There were children with pre-existing condition potentially affecting respiration but all were stable and asymptomatic at the time of testing. Therefore, we feel the work of breathing was not significantly altered by the surgical procedure or intraoperatively administered narcotic medications. We examined nine factors (gender, age, pre-existing condition affecting respiration, pre-operative temperature, BMI, Relative percent change on mean arterial pressure between preoperative and postoperative value, heart rate and Respiratory rate at PACU arrival, and mask size) and four different time points of $PexCO_2$ measurement for association with measurement error. BMI was the only significant factor for predicting measurement error at 20-30 seconds ($p=0.035$). However, our data only contain BMI lower than 25 meaning no obese children were involved in our study. In adult study by Kasuya Y et al., accuracy in non-obese and obese patients, with and without OSA, was similar in arterial-to-end-tidal partial pressure difference in mainstream capnography [9].

We tested mainstream capnography mask system to detect hypercapnia [Table/Fig-3]. Using $PcvCO_2$ of 50 mmHg and $PexCO_2$ of 45 mmHg as hypercapnia threshold, the AUC was 0.809 to 0.866 at each time points of peak exhaled CO_2 measurement. Mainstream mask capnography seems useful device to discriminate hypercapnia in non-intubated children.

LIMITATION

There are several potential limitations to the study. There are a limited number of children with relatively minor respiratory problems; however, there were strong correlations between measurements and the Bland-Altman plots did not show any systematic bias at any time points of peak exhaled CO_2 measurement including hypercapnic children. We were able to compare only the exhaled CO_2 values to central venous blood gas at one oxygen flow rate but from our prior study a higher flow rate did not provide a significantly greater amount of bias (2 vs 5 L/minute flow). The difference in average CO_2 values between O_2 flow rates of 2 L/minute and 5 L/minute was 1.2 mmHg.

CONCLUSION

This is the first study to assess the accuracy of a mainstream mask capnography system specifically designed for children with different body weights to central venous PCO_2 . We conclude that mainstream

mask capnography is a reliable device to assess hypoventilation and hypercapnia in non-intubated children.

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