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TITLE:

Evaluation of Capnography Sampling Line Compatibility and Accuracy when Used with a Portable Capnography Monitor

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KEYWORDS:
accuracy, capnography, continuous respiratory monitoring, $ETCO_2$, respiratory rate, sampling line, supplemental oxygen

SUMMARY:

The goal of this study was to evaluate the accuracy of capnography sampling lines used in conjunction with a portable bedside capnography monitor. Sampling lines from 7 manufacturers were evaluated for tensile strength, rise time, and $ETCO_2$ accuracy as a function of respiratory rate or supplemental oxygen flow rate.

ABSTRACT:

Capnography is commonly used to monitor patient's ventilatory status. While sidestream capnography has been shown to provide a reliable assessment of end-tidal CO_2 ($ETCO_2$), its accuracy is commonly validated using commercial kits composed of a capnography monitor and its matching disposable nasal cannula sampling lines. The purpose of this study was to assess the compatibility and accuracy of cross-paired capnography sampling lines with a single portable bedside capnography monitor. A series of 4 bench tests were performed to evaluate the tensile strength, rise time, $ETCO_2$ accuracy as a function of respiratory rate, and $ETCO_2$ accuracy in the presence of supplemental O_2. Each bench test was performed using specialized, validated equipment to allow for a full evaluation of sampling line performance. The 4 bench tests successfully differentiated between sampling lines from different commercial sources and suggested that due to increased rise time and decreased $ETCO_2$ accuracy, not all nasal cannula sampling lines provide reliable clinical data when cross-paired with a commercial capnography monitor. Care should be taken to ensure that any cross-pairing of capnography monitors and disposable sampling lines is fully validated for use across respiratory rates and supplemental O_2

flow rates commonly encountered in clinical settings.

INTRODUCTION:

Capnography is a commonly used technology designed to assess the integrity of a patient's ventilatory status by measuring the patient's end-tidal CO_2 ($ETCO_2$) and respiratory rate[1]. When used in combination with pulse oximetry, a more comprehensive assessment of respiratory function can be achieved[2,3]. Capnography is frequently used in the post-anesthesia care unit, in intubated or deeply sedated patients[4], in the intensive care unit (ICU), and in the emergency department[5]. In fact, the American Society of Anesthesiologists (ASA)[6,7] recommends continuous capnography during all general anesthesia procedures[8] and during moderate and deep sedation, which included an estimated 106 million procedures in the United States from January 2010-December 2014[9,10].

Inherent in the use of capnography is reliance on a device that provides the clinician with an accurate assessment of a patient's ventilatory status. Capnography monitoring can be either sidestream, in which exhaled breath is diverted to a monitor by a nasal cannula and tubing, or mainstream, in which exhaled breath is measured at the source without diverting the sample[11]. Mainstream capnography is most often used in intubated patients, whereas sidestream capnography is used for both intubated and non-intubated patients[12]. One important component of sidestream capnography is the sampling line, which delivers CO_2 from a patient's exhaled breath to the detector, where breath analysis occurs[1,13]. Commercial sampling line designs vary significantly, with differences in sampling line connection points, nasal cannula shapes, and tubing volumes, all of which can affect sampling line performance[13,14]. For example, nasal cannula sampling lines can have up to 10 connections between the nasal cannula, humidifier, $ETCO_2$ sampling line, and O_2 delivery tubes (**Figure 1**). Each of these connections represents a potential weak point in the monitoring system.

The performance of nasal cannula sampling lines can be evaluated by a variety of tests such as the overall weak point and rise time. In addition, they can be tested to determine the impact of respiratory rate and the delivery of supplemental oxygen on $ETCO_2$ readings. Although previous studies have reported $ETCO_2$ accuracy on a limited number of sampling lines[15-23], there are no known studies that have evaluated nasal cannula capnography sampling line performance using a combination of tests, such as identification of the overall weak point, measurement of rise time, and determination of $ETCO_2$ accuracy.

The overall weak point of a sampling line can be measured using a tensile strength test, in which each connection point is tested for how much force is exerted on the connection before it reaches a breaking point. The tensile strength test can identify the weakest connection point for a medical device, allowing direct comparisons between unique device designs. This style of strength test is often performed on medical devices, ranging from pacing leads to catheters[24,25]. Since capnography sampling lines have a large number of tubing connection points, the weakest connection point can differ depending on the device design. The tensile strength of connection points is particularly important in mobile environments such as ambulances, where sampling lines can be pulled apart unintentionally due to space constraints. Capnography sampling lines can also become unintentionally disconnected in hospital rooms, where multiple monitoring systems are often simultaneously connected to a patient, and the equipment lines can become tangled and pulled on by either a mobile patient or a healthcare provider. In both scenarios, the tension applied to the sampling line can result in a loss of capnography data and in some instances, interruption of supplemental O_2 delivery.

Another critical element of sidestream capnography monitoring affected by sampling line design is rise time, defined as the time required for a measured CO_2 value to increase from 10% to 90% of the final value[14]. The rise time is a direct indicator of the system resolution, defining how well individual breaths are separated from one another during sampling (**Figure 2A**). In practice, a shorter rise time is preferable to a long rise time. This is due to the potential mixing of multiple breath samples in capnography systems with long rise times, resulting in inaccurate $ETCO_2$ measurements[14]. Importantly, rise time is affected by both breath flow and sampling line design, due to the friction of air moving along the tubing, the presence of filters, and the volume of dead space within the sampling line. Sampling lines with more dead space have reduced breath sample resolution, resulting in mixed breath $ETCO_2$ waveforms, and as a result, inaccurate $ETCO_2$ readings[13,14]. These poorly differentiated breath samples occur most often in patients with a rapid respiratory rate, including infants and children[14-16].

$ETCO_2$ measurements can also be impacted by respiratory rate and the delivery of supplemental oxygen[15,26-28]. Although changes in minute ventilation and presence of respiratory depression can be easily detected with a capnograph[27,28], there is scarce data on specific performance of nasal cannula capnography sampling lines at different respiratory rates. A recent study found that during steady breathing, respiratory rate measured by a respiratory volume monitor and capnograph were strongly correlated ($R = 0.98 \pm 0.02$) and consistent for all breathing rates, including normal, slow, and fast breathing rates[28]. Regarding use of supplemental oxygen, a separate study compared $ETCO_2$ readings in healthy volunteers in the presence of pulsed or continuous oxygen flow, using between 2 and 10 L/min oxygen[17]. While the pulsed oxygen flow had a limited impact on measured $ETCO_2$ (median 39.2 mmHg), continuous oxygen flow, which is standard in clinical settings, resulted in a wide range of $ETCO_2$ measurements (median 31.45 mmHg, range 5.4 to 44.7 mmHg) that were clinically different from $ETCO_2$ readings in the absence of supplemental oxygen[17]. In addition, differences in $ETCO_2$ measurements in the presence of supplemental oxygen flow have been compared across nasal cannula designs[15,18]. In contrast to nasal cannulas with oral scoops, one study found that some cannulas failed to deliver exhaled CO_2 to the capnometer in the presence of 10 L/min O_2[18]. Another study reported that while $ETCO_2$ readings with supplemental oxygen during simulated normal ventilation were normal, $ETCO_2$ readings were reduced in the presence of supplemental oxygen during simulated hypoventilation and hyperventilation[15]. This is consistent with evidence that $ETCO_2$ accuracy is more difficult to achieve when the flow rate of CO_2 in exhaled breath is similar to the flow rate of supplemental oxygen, due to dilution of the exhaled CO_2 (**Figure 2B**)[20].

The accuracy of $ETCO_2$ readings has been evaluated in multiple independent studies, all of which concluded that capnography offered a reliable measure of ventilation status[16,18-22]. However, few studies have compared the accuracy of different sidestream capnography systems, and although capnography sampling lines are used with a variety of commercial capnography monitors, the accuracy of these cross-paired devices is not well-described[23]. Thus, determining whether alternative commercial sampling lines are compatible with capnography monitors and provide accurate data is important for healthcare providers who use this equipment to monitor patient ventilation.

The purpose of this study was to determine the compatibility and accuracy of commercially available sidestream capnography sampling lines used in conjunction with a portable capnography monitor. A series of four bench tests were performed using specially designed, validated systems to compare the performance of a series of capnography sampling lines with a single respiratory monitor. The four major outcomes of the study included (1) tensile strength and identification of the weak connection point for each capnography sampling line; (2) rise time; (3) $ETCO_2$ accuracy as a function of respiratory rate; and (4) $ETCO_2$ accuracy in the presence of supplemental oxygen.

PROTOCOL:

The capnography sampling lines used in these bench tests included 16 adult, pediatric, and neonatal capnography sampling lines from 7 commercial sources. Among the 16 sampling lines included in the bench tests, 5 sampling lines were from the same manufacturer as the capnography monitor utilized for the bench tests ('matched'), and 11 sampling lines were from alternate manufacturers ('cross-paired') (Table of Materials). All of the nasal cannula sampling lines share a similar design, with up to 10 connection points between the cannula, humidifier, O_2 connector, CO_2 connector, 4-way, O_2 tube, and CO_2 tube (Figure 1).

1. Measure sampling line tensile strength

1.1 Calibrate the tensile testing jig.

1.1.1 In the tensile testing jig software, set the load cell selection to 100.00 kg and the load parameter to 10.00 kg.

1.2 Attach sampling line components (example: O_2 connector with O_2 tube) to the calibrated tensile testing jig.

1.3 Starting with a mass of 0 kg, initiate tension on the sampling line component and observe whether the sampling line connection remains intact.

1.4 If the sampling line connection remains intact, automatically increase the mass in a continuous manner, and observe when the subparts break or disconnect.

NOTE: The resolution of the jig is limited to 10 g increments.

1.5 Record the maximum tension (kg) exerted before the sampling line break occurred.

1.6 Repeat the tensile strength test for all 10 potential sampling line subparts: O_2 connector with O_2 tubing; O_2 tubing with 4-way; 4-way with O_2 tubing; O_2 tubing with cannula; cannula with CO_2 tubing; CO_2 tubing with 4-way; 4-way with CO_2 tubing; CO_2 tubing with CO_2 connector; humidifier with tubing; tubing with cannula.

1.7 Repeat the tensile strength test on 16 sampling lines from 7 commercial sources.

2. Measure rise time and sampling line accuracy

2.1 Calibrate the rise time measurement device.

2.1.1 Cut standard 0.95 mm internal diameter CO_2 PVC tube into ten 15 cm pieces.

2.1.2 Operate the jig using the following steps:

2.1.2.1 Turn on the air compressor, jig controller, and power supply.

2.1.2.2 Open the CO_2 gas flow.

2.1.2.3 Attach the sampling channel directly to the measurement chamber without the sample.

2.1.2.4 Calibrate the air and CO_2 flow to 10 L/min and the gas sampling rate to 50 mL/min using a mass flow meter and a dedicated restrictor.

NOTE: The maximum sampling rate of the capnography monitor is 50 mL/min.

2.1.2.5 Open the jig software and define the test parameters as follows: Air:CO_2 ratio 1:1; Air time = 3 seconds, CO_2 time = 3 seconds, 10 cycles, rise time measurement length: none.

2.1.2.6 Open the CO_2 valve.

2.1.2.7 Select the **Finish Calibration** button on the **Measurement** tab and make sure it turns green.

2.1.2.8 Select the **Measure** button and wait for the gas flow cycles to end.

2.1.2.9 Close the CO_2 valve.

2.1.3 Record the background rise time and ensure the result is less than 60 ms. If it is larger, clean the optical chamber with air flow and re-connect the y-piece/airway adapter properly.

2.1.4 Take 10 measurements and calculate the average rise time value.

2.1.5 Compare the rise time value to the margins and confirm it is inside the specification limits, pre-defined as rise time background < 60 ms and rise time of a control sample, a 15 cm PVC tube, 0.95 mm internal diameter, equal to 39 ± 5 ms.

2.1.6 Compare the delivery time to the margins and confirm it is inside the specification limits, predefined as background delivery time <100 ms and delivery time of a control sample, a 15 cm PVC tube, 0.95 mm internal diameter, equal to 152 ± 5 ms.

2.2 Open a new commercial sampling line.

2.3 Connect the sampling line to the rise time measurement device.

2.4 Click on the **Start** button in the rise time measurement device software and wait for the device to measure the rise time.

NOTE: The device repeats the measurement 10 times and automatically averages the repeats to report the rise time mean and standard deviation.

2.4.1 Copy the rise time result to the report.

2.5 Disconnect the sampling line from the rise time measurement device.

2.6 Calculate maximum respiratory rate for inhalation:exhalation time ratios of 1:1 and 1:2, in breaths per minute (BPM).

2.6.1 Calculate the maximum respiratory rate using the measured rise time for the sampling line and a 1:1 breath ratio, using the following equation:

$$Maximum\ Respiratory\ Rate\ (BPM) = 30\ \mathrm{s} \div Rise\ time\ for\ sampling\ line\ (\mathrm{s})$$

where 30 s represents the cumulative time used to exhale during 1 min (1:1 inhalation:exhalation time).

NOTE: For a 1:1 breath ratio, the maximum respiratory rate represents the fastest allowed respiratory rate without impacting $ETCO_2$ accuracy when the time required for inhalation and exhalation is the same.

2.6.2 Calculate the maximum respiratory rate using the measured rise time for the sampling line and a 1:2 breath ratio, using the following equation:

$$Maximum\ Respiratory\ Rate\ (BPM) = 40\ \mathrm{s} \div Rise\ time\ for\ sampling\ line\ (\mathrm{s})$$

where 40 s represents the cumulative time used to exhale during 1 min (1:2 inhalation:exhalation time).

NOTE: For a 1:2 breath ratio, the maximum respiratory rate represents the fastest allowed respiratory rate without impacting $ETCO_2$ accuracy when the time used to exhale is twice as long as the time used to inhale.

2.7 Calculate exhalation time for inhalation:exhalation time ratios of 1:1 and 1:2.

2.7.1 For a 1:1 breath ratio, use the following equation:

$$Exhalation\ Time\ (\mathrm{sec}) = 30\ \mathrm{s} \div Maximim\ respiratory\ rate\ for\ 1:1\ breath\ ratio\ (BPM)$$

where 30 s represents the cumulative time used to exhale during 1 min (1:1 inhalation:exhalation time).

2.7.2 For a 1:2 breath ratio, use the following equation:

$$Exhalation\ Time\ (sec) = 40\ \mathrm{s} \div Maximum\ respiratory\ rate\ for\ 1:2\ breath\ ratio\ (BPM)$$

where 40 s represents the cumulative time used to exhale during 1 min (1:2 inhalation:exhalation time).

2.8 Determine the accuracy of each sampling line at 150 BPM for 1:1 and 1:2 breath ratios by evaluating the maximum respiratory rate.

NOTE: If the maximum respiratory rate is ≥150 BPM, then the sampling line is considered accurate for the breath ratio, but if the maximum respiratory rate is <150 BPM, then the sampling line is not considered accurate at 150 BPM.

2.9 Repeat steps 2.2-2.8 for all 16 sampling lines tested.

3. Perform statistical analysis using statistical software.

3.1 Compare mean and standard deviation using Student's t-test, with a two-sided significance level of 0.05, for all capnography monitor matched sampling lines vs. all capnography monitor cross-paired sampling lines.

3.2 Repeat statistical analysis to compare all capnography monitor matched pediatric sampling lines to all capnography monitor cross-paired pediatric sampling lines.

3.3 Repeat statistical analysis to compare all capnography monitor matched adult sampling lines to all capnography monitor cross-paired adult sampling lines.

4. Measure $ETCO_2$ accuracy as a function of respiratory rate

4.1 Prepare the manikin by placing in a supine position and connect the sampling line to the manikin per manufacturer instructions.

4.2 Attach the sampling line to the capnography monitor and change the capnography monitor setting to accept sampling lines from all manufacturers by selecting **Settings** and **Cancel Gold Ring Identification**.

4.3 Prepare and calibrate the breath simulator jig, to control the simulated respiratory rate.

NOTE: The breath simulator jig is composed of a 2-way electrical operating valve, allowing for precise control of the flow of CO_2 and N_2 to the manikin, to simulate human breathing.

4.3.1 Use a flow meter to measure the gas flow and calibrate it to 10 L/min.

4.3.2 Open the breath simulator jig software and set the duty cycle to 50%.

4.3.3 Test for leaks in the system using a leak testing jig.

4.3.3.1 Connect the sampling line to the CO_2 port on the leak testing jig.

4.3.3.2 Create a kink in the sampling line to prevent CO_2 from exiting the end of the sampling line.

4.3.3.3 Using a flow rate of 50 mL/min CO_2, allow the pressure in the sampling line to increase to 300 mmHg, and then stop adding CO_2.

4.3.3.4 Observe if the pressure in the sampling line remains the same or decreases. If the pressure decreases, this confirms a leak in the system, and a new sampling line should be applied in Step 4.2.

4.3.4 Connect the breath simulator jig to the manikin.

4.4 Increase the 5% CO_2 flow rate to 10 L/min and the N_2 flow rate to 10 L/min using the breath simulator jig. Keep flow rates constant throughout the test.

4.5 Wait 30 seconds to allow a steady capnography waveform to be established, then record the $ETCO_2$ value (mmHg).

4.6 Measure a total of 10 $ETCO_2$ values over 180 seconds.

4.7 Change the respiration rate using the breath simulator jig, allow the capnography waveform to normalize for 30 seconds, and record 10 $ETCO_2$ readings over 180 seconds.

4.7.1 Repeat readings for each respiratory rate examined: 10, 20, 40, 60, 80, 100, 120, and 150 BPM.

4.8 Determine the average and standard deviation of the 10 measured readings at each respiratory rate.

4.9 Repeat steps 4.1-4.8 for all 16 sampling lines tested.

4.10 Perform statistical analysis using Bland-Altman graphical plots to evaluate sampling line bias.

5. Measure $ETCO_2$ accuracy in the presence of supplemental O_2

5.1 Prepare the manikin and breath simulator jig as described in Steps 4.1-4.3. Set the breath simulator jig to 10 BPM.

5.2 Connect the O_2 line to 100% O_2.

5.3 Increase the CO_2 flow rate to 6 L/min and the O_2 flow rate to 0 L/min, to use as a reference measurement.

5.4 To allow the capnography waveform to stabilize, wait 30 seconds before recording the $ETCO_2$ value.

5.5 Read the $ETCO_2$ value 10 times over 180 seconds.

5.6 Change the flow rate of the CO_2 and O_2, allow the capnography waveform to normalize for 30 seconds, and repeat the 10 $ETCO_2$ measurements over 180 seconds. To capture common clinical scenarios, use the following combinations of CO_2 and O_2 flow rates:

5.6.1 Use a combination of 2 L/min CO_2 and 2 L/min O_2.

5.6.2 Use a combination of 4 L/min CO_2 and 2 L/min O_2.

5.6.3 Use a combination of 4 L/min CO_2 with 4 L/min O_2.

5.6.4 Use a combination of 6 L/min CO_2 with 4 L/min O_2.

5.6.5 Use a combination of 6 L/min CO_2 with 6 L/min O_2.

5.6.6 Use a combination of 8 L/min CO_2 with 6 L/min O_2.

5.7 Repeat the test as described in 5.1-5.6 for each sampling line.

5.8 Perform statistical analysis using Bland-Altman graphical plots to evaluate sampling line bias.

REPRESENTATIVE RESULTS:

Tensile strength

Sixteen capnography sampling lines from 7 manufacturers were tested to determine the tensile strength of each major sampling line joint (**Figure 1**, **Table of Materials**). Due to differences in sampling line design, not all joints exist in all sampling lines. The capnography monitor matched sampling lines 8, 9, 14, 15, and 16 had minimum overall tensile strengths between 3.55 kg and 5.94 kg. Most cross-paired sampling lines exhibited similar overall tensile strengths (**Table 1**). Sampling line 6 had the weakest tensile strength, with tensile strength equal to 1.33 kg at the connection between the CO_2 tube and the 4-way. Common weak points among all sampling lines included the connection between the CO_2 tubing and the 4-way, and the connection between the cannula and the CO_2 tube.

Rise time

The rise time, defined as time required for the measured CO_2 value to increase from 10% to 90% of the final value (Figure 2), was determined for the same 16 capnography sampling lines (Table of Materials). Comparison of capnography monitor matched vs cross-paired sampling lines found that the rise time for all cross-paired sampling lines was significantly higher (147 ± 23 ms vs. 201 ± 66 ms, respectively; $p<0.001$). A significant difference was also present between adult matched and cross-paired sampling lines (135 ± 13 ms vs. 214 ± 61 ms; $p<0.001$) but not between pediatric matched and cross-paired sampling lines (156 ± 25 ms vs. 169 ± 69 ms; $p=0.395$). Based on the measured rise time for each sampling line, the maximum respiratory rate (BPM), and exhalation time, using an inhalation: exhalation ratio of 1:1 and 1:2, the accuracy of each sampling line at 150 BPM was determined. While a majority of the sampling lines exhibited accuracy at 150 BPM for both breathing ratios, sampling lines 2, 3, 6, 7, 12, and 13 each failed to maintain accuracy at 150 BPM, whereas sampling lines 1, 4, 5, 8, 9, 10, 11, 14, 15, and 16 maintained accuracy in all tested conditions (**Table 2**). In particular, sampling lines 3, 6, and 13 all failed to meet the accuracy standard at 150 BPM in both the 1:1 and 1:2 inhalation:exhalation ratios.

$ETCO_2$ accuracy as a function of respiratory rate

Accuracy of $ETCO_2$ was measured using respiration rates between 10 and 150 BPM for 16 sampling lines from 7 manufacturers (**Table of Materials**). The expected $ETCO_2$ in the presence of 5% CO_2 was 34 mmHg at ambient pressure, and the range predefined as acceptable accuracy was ±2 mmHg for readings between 0-38 mmHg and ±5% of the reading + 0.08 for every 1 mmHg above 38 mmHg. Among the adult sampling lines tested, at 10 BPM, sampling lines 8 and 9 read $ETCO_2$ equal to 33-34 mmHg (**Figure 3A**). Sampling lines 2, 5, 6, and 7 also read $ETCO_2$ levels within an acceptable range (31-34 mmHg) at the lowest respiration rates (10-20 BPM). In contrast, sampling lines 3 and 4 reported low $ETCO_2$ levels at the lowest respiration rate (10 BPM), and these readings decreased to 0 mmHg when the respiration rate increased to 80 BPM or higher. Only sampling lines 1, 8, and 9 continued to capture readings at very high respiration rates (120-150 BPM); sampling lines 2, 3, 4, 5, 6, and 7 read $ETCO_2$ values equal to 0 mmHg at very high respiration rates (≥100 BPM). A similar pattern was observed in the pediatric and neonatal sampling lines, in which sampling lines 10, 11, 14, 15, and 16 captured readings across all respiration rates, and sampling lines 12 and 13 reported $ETCO_2$ equal to 0 mmHg at respiration rates ≥100 BPM (**Figure 3B**). The bias of the $ETCO_2$ readings was confirmed using Bland-Altman plots for capnography monitor matched and cross-paired sampling lines, where a majority of the $ETCO_2$ measurements were within 95% limits, but the matched sampling lines exhibited higher accuracy with a bias toward overestimating $ETCO_2$ at 150 BPM, and the cross-paired sampling lines strongly underestimated $ETCO_2$ measures when respiratory rate was 80 BPM or higher (**Figure 4A-B**).

$ETCO_2$ accuracy in the presence of supplemental oxygen

In addition to examining the accuracy of $ETCO_2$ values of commercial sampling lines from 7 manufacturers (**Table of Materials**) as a function of respiratory rate, their accuracy was also evaluated in the presence of 2, 4, or 6 L/min supplemental oxygen (**Figure 5**), which represent the range of supplemental oxygen flow rates commonly used in clinical settings.[3,29] In all cases, the expected $ETCO_2$ was 34 mmHg. In the absence of supplemental oxygen, $ETCO_2$ values were

34 ± 0 mmHg for sampling lines 8 and 9, and as low as 16 ± 0 mmHg for sampling lines 3, 4, and 12 (**Figure 5A**). Upon the addition of 2 L/min supplemental oxygen, a majority of sampling lines exhibited a decrease in observed $ETCO_2$ values, ranging between 0 ± 0 mmHg and 23 ± 1 mmHg; sampling lines 7, 8, and 9 reported $ETCO_2$ values between 33 ± 0 mmHg and 34 ± 0 mmHg (Figu**re 5B**). The most extreme drop in $ETCO_2$ value occurred in sampling line 2, which measured $ETCO_2$ of 0 mmHg in the presence of as little as 2 L/min supplemental oxygen; this was also observed in sampling lines 2 and 5 in the presence of 4 and 6 L/min supplemental oxygen (**Figure 5C-D**). Decreased $ETCO_2$ accuracy was also observed in sampling lines 1, 6, 10, 11, and 13 in the presence of 2, 4, or 6 L/min supplemental oxygen (**Figure 5B-D**). Bland-Altman plots for capnography monitor matched and cross-paired sampling lines indicate that while the matched sampling lines had high precision and limited bias in reading $ETCO_2$ levels in the presence of supplemental oxygen, the cross-paired sampling lines consistently underestimated $ETCO_2$ in the presence of supplemental oxygen (**Figure 6A-B**).

FIGURE AND TABLE LEGENDS:

Table 1: Tensile strength test of capnography sampling lines.

Table 2: Rise time for capnography sampling lines when used in conjunction with a portable capnography monitor. The rise time for each sampling line was measured 10 times to ensure accuracy of results.

Figure 1: Capnography sampling line design.

Figure 2: Fundamentals of sidestream capnography. (A) Example design of a sampling line, demonstrating how exhaled CO_2 is sampled by the device. **(B)** Typical correlation between breathing flow rate (black line) and $ETCO_2$ (green line) as function of time. A constant supplemental O_2 flow is represented by a blue dashed line. Accurate measurement of $ETCO_2$ occurs when CO_2 has peaked (green dashed line). Inaccurate $ETCO_2$ measurements (red dashed lines) can occur later in the breath cycle, when CO_2 is diluted with supplemental O_2. This occurs most often when the CO_2 exhalation flow rate is equal to the flow of supplemental O_2.

Figure 3: $ETCO_2$ accuracy of adult and pediatric capnography sampling lines as a function of respiration rate. Measured $ETCO_2$ values for **(A)** Adult and **(B)** Pediatric and Neonatal capnography sampling lines across a range of respiratory rates from 10 to 150 BPM. In all cases, the expected $ETCO_2$ value is 34 mmHg.

Figure 4: Bland-Altman plot for $ETCO_2$ measures by (**A)** Matched sampling lines as a function of increasing respiratory rate and **(B)** Cross-paired sampling lines as a function of increasing respiratory rate.

Figure 5: $ETCO_2$ accuracy of capnography sampling lines in the presence of increasing supplemental oxygen. $ETCO_2$ accuracy is reported for **(A)** No supplemental oxygen; **(B)** 2 L/min supplemental oxygen; **(C)** 4 L/min supplemental oxygen; and **(D)** 6 L/min supplemental oxygen. The green line at 34 mmHg represents the expected $ETCO_2$ value across all measurements.

Figure 6: Bland-Altman plot for $ETCO_2$ measures by (A) Matched sampling lines as a function of increasing supplemental O_2 flow rate; (**B)** Cross-paired sampling lines as a function of increasing supplemental O_2 flow rate.

DISCUSSION:

A series of four bench tests were performed to compare the accuracy and compatibility of matched and cross-paired capnography sampling lines with a portable capnography monitor. These calibrated tests measured average rise time and $ETCO_2$ levels across 10 independent repeat measures for each of the 16 sampling lines tested, and identified minimal variation in the results. While the tensile strength of the commercial sampling lines remained within the product specifications, the rise time differed significantly between capnography monitor matched and cross-paired sampling lines ($p<0.001$), and $ETCO_2$ accuracy as a function of respiratory rate and in the presence of supplemental O_2 was higher in capnography monitor matched sampling lines as opposed to cross-paired sampling lines. In particular, several of the cross-paired adult and pediatric sampling lines had rise times considered inaccurate at a maximum respiratory rate 150 BPM. The same sampling lines exhibited poor $ETCO_2$ accuracy at high respiratory rate or in the presence of supplemental oxygen.

The tensile strength test utilized a calibrated tensile testing jig to successfully measure tension across capnography sampling line components ranging from 1.33 to 26.6 kg. Although tensile strength tests are often performed on other types of medical devices[24,25], our method was unique in that it examined the tensile strength of each segment of the capnography sampling line. Therefore, in addition to determining the tensile strength of each sampling line component, it also allowed for identification of the overall weak point of the complete sampling line. The test results confirmed that nearly all of the sampling lines do meet product specifications, pre-defined as withstanding a force of 2 kg. One limitation of this testing system is the continuous, gradual increase in force applied to the sampling line, as opposed to a sudden strong force, which could be encountered in clinical settings. Importantly, as a validated instrument, the jig used to measure the tensile strength of the capnography sampling lines could be used for other applications, such as measuring the tensile strength of other sampling tubes and medical devices that have the potential to experience tension in a clinical setting.

Rise time is an important technical feature of sidestream capnography sampling lines and determines their ability to provide a precise, high resolution reading of CO_2 in exhaled breath[1,14]. Due to the importance of this technical feature, we sought to measure the rise time using a validated rise time measurement device, so that the maximum respiratory rate and exhalation time could be calculated. We needed to modify the rise time measurement parameters to remove the upper time limit on the rise time jig, so that the rise time could be collected for all sampling lines before the measurement period ended. The long rise time observed for some capnography sampling lines could reflect an increased volume of dead space in these sampling lines. Importantly, as part of this method, we determined the maximum respiratory rate and exhalation time for two unique breathing patterns, defined by inhalation:exhalation ratios equal to 1:1 and 1:2. This unique aspect of the analysis allowed evaluation of the accuracy of measured

CO_2 in circumstances that represent patients whose breathing pattern is uniform or whose exhalation time lasts longer than their inhalation time. In sampling lines in which the calculated maximum respiratory rate was >150 BPM, we concluded that the sampling line was accurate. Although a rapid breathing rate of 150 BPM is unlikely to be encountered clinically, we determined the accuracy of each sampling device at this high breath rate because it is considered the technical upper limit for many capnography sampling lines. While a respiratory rate of 150 BPM is non-physiologic, the bench test highlights that while some capnography sampling lines were accurate across the full technical range of respiratory rates, other sampling lines failed to achieve the same accuracy standard. Compared to the capnography monitor matched sampling lines, some of the cross-paired sampling lines, including sampling lines 2 and 7, failed to achieve accuracy at 150 BPM for the 1:1 inhalation:exhalation ratio, and sampling lines 3, 6, and 13 failed to achieve the accuracy standard at 150 BPM for both inhalation:exhalation ratios. This could be due to a larger dead space within the sampling lines, which results in a longer rise time and a mixing of breath samples.

To apply the rise time findings to a clinical setting, we performed two tests to examine $ETCO_2$ accuracy when sampling lines were connected to a portable capnography monitor via a manikin. For both tests, we needed to modify the default capnography monitor settings to allow the monitor to recognize cross-paired sampling lines. First, similar to a previous study, we controlled respiratory rate using a respiratory rate controller, and monitored the resulting $ETCO_2$ measurements for each sampling line[18]. A key component of this test was the use of a pre-defined set of respiratory rates ranging from 10 to 150 BPM, to determine $ETCO_2$ accuracy across respiratory patterns that patients could exhibit. While the expected $ETCO_2$ level was 34 mmHg in all circumstances, we observed many instances in which, as respiratory rate increased, sampling lines no longer reported accurate $ETCO_2$ readings, but instead, dropped to 0 mmHg, which is not a clinically meaningful result. In fact, only sampling lines 1, 8, 9, 10, 15, and 16 did not measure $ETCO_2$ values of 0 mmHg at any respiratory rate. This accuracy could be due to the design of the sampling lines, such that those with higher friction or larger dead space volume result in lower resolution breath samples at increased respiratory rate, similar to what we observed in the rise time test. While the sampling lines with high $ETCO_2$ readings may contain less dead space that enable them to deliver discrete breath samples, the error of $ETCO_2$ readings above 38 mmHg was pre-defined as ±5% of the reading + 0.08 for every 1 mmHg above 38 mmHg. This could partially explain why the $ETCO_2$ readings were increased above 34 mmHg during high respiratory rate in some sampling lines. In contrast, the sampling lines with low or zero $ETCO_2$ readings may contain more dead space, resulting in mixed breath samples that the capnography monitor does not recognize as valid breaths, and thus reports as no breath. Importantly, 3 of the cross-paired sampling lines from one manufacturer did not exhibit accurate $ETCO_2$ readings at any respiratory rate tested between 10 and 150 BPM, suggesting that it does not provide clinically reliable ventilatory information when cross-paired with the capnography monitor used in the test (**Table of Materials**). Together, these observations suggest that devices with a longer rise time have a lower maximum accurate respiration rate and exhibit low $ETCO_2$ accuracy at the maximum accurate respiration rate.

In the second test of $ETCO_2$ accuracy using a manikin, we maintained a constant respiratory rate but introduced the flow of supplemental oxygen to the system. This test mimics a common occurrence in hospital settings in which patients being monitored by sidestream capnography receive supplemental oxygen, and where $ETCO_2$ accuracy is key in understanding a patient's respiratory function, as supplemental oxygen can mask ventilation challenges due to high oxygen saturation readings from pulse oximetry[30,31]. Similar to the $ETCO_2$ accuracy test with varying respiratory rate, in this test, a key step in the protocol was to measure $ETCO_2$ accuracy across multiple supplemental oxygen flow rates. The main limitation of the $ETCO_2$ tests is that the tests are performed using a manikin and a controlled breathing system, as opposed to a human subject, in which breathing patterns vary between individuals. In a control reading without supplemental O_2, we observed that sampling lines 3, 4, and 12, all from the same manufacturer, failed to report the expected $ETCO_2$ value of 34 mmHg, and only sampling lines 8, 9, and 11 reported this value. In the presence of 2, 4, or 6 L/min supplemental O_2, a majority of the sampling lines exhibited reduced $ETCO_2$ accuracy, with the exception of the matched sampling lines 8 and 9 and the cross-paired sampling line 7. In particular, similar to our observations upon increase of the respiratory rate, the $ETCO_2$ readings for sampling lines 2 and 5 dropped to 0 mmHg in the presence of supplemental O_2, suggesting that their $ETCO_2$ accuracy when cross-paired with a capnography monitor is very low. This may be due to the design of the sampling lines, and in particular, the nasal cannula design, which is designed to both deliver oxygen to a patient and collect breath samples from a patient. If the nasal cannula contains a large amount of dead space, mixing of the supplemental oxygen and the exhaled breath can occur, resulting in low amplitude, mixed breaths that the capnography monitor does not detect as exhaled breath. In such a case, the ETCO2 measurement would drop to zero, as we observed with some of the cross-paired sampling lines tested.

Similar to previous studies examining the accuracy of capnography, we successfully identified circumstances where the $ETCO_2$ accuracy using a variety of sampling lines was acceptable, including cases in which there was a moderate respiratory rate or when no supplemental O_2 was used[19-23,32]. Importantly, many of the sampling lines failed to maintain $ETCO_2$ accuracy upon an increase in respiratory rate or upon the introduction of supplemental O_2, which is consistent with previous assessments of capnography accuracy[15,18,20,23]. Together, the findings are consistent with previous bench tests that successfully measure the accuracy of capnography sampling lines[15,18]. Given that many of the sampling lines cross-paired to the capnography monitor exhibited reduced $ETCO_2$ accuracy in clinically relevant circumstances, care should be taken to ensure that any cross-paired commercial sampling lines and monitors are validated before being used to monitor patient ventilation status.

ACKNOWLEDGMENTS:
This work was funded by Medtronic. Marco Scardapane (Medtronic Study and Scientific Solutions MC2, Rome, Italy) performed statistical analysis.

DISCLOSURES:
Ruben D. Restrepo is a consultant for Medtronic, and Ido Karpenkop and Katherine E. Liu are employees of Medtronic.

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Figure 1


O2 Connector
Cannula
CANNULA ↓ CO2 TUBE
TUBE ↓ CANNULA CONNECTION
O2 CONNECTOR ↓ O2 TUBE
4 Way
4 WAY ↓ O2 TUBE
O2 TUBE ↓ 4 WAY
O2 Tube
HUMIDIFIER ↓ TUBE CONNECTION
4 WAY ↓ CO2 TUBE
CO2 TUBE ↓ 4WAY
CO2 Tube
Humidifier
CO2 TUBE ↓ CO2 CONNECTOR
O2 TUBE ↓ CANNULA
CO2 Connector

Figure 2

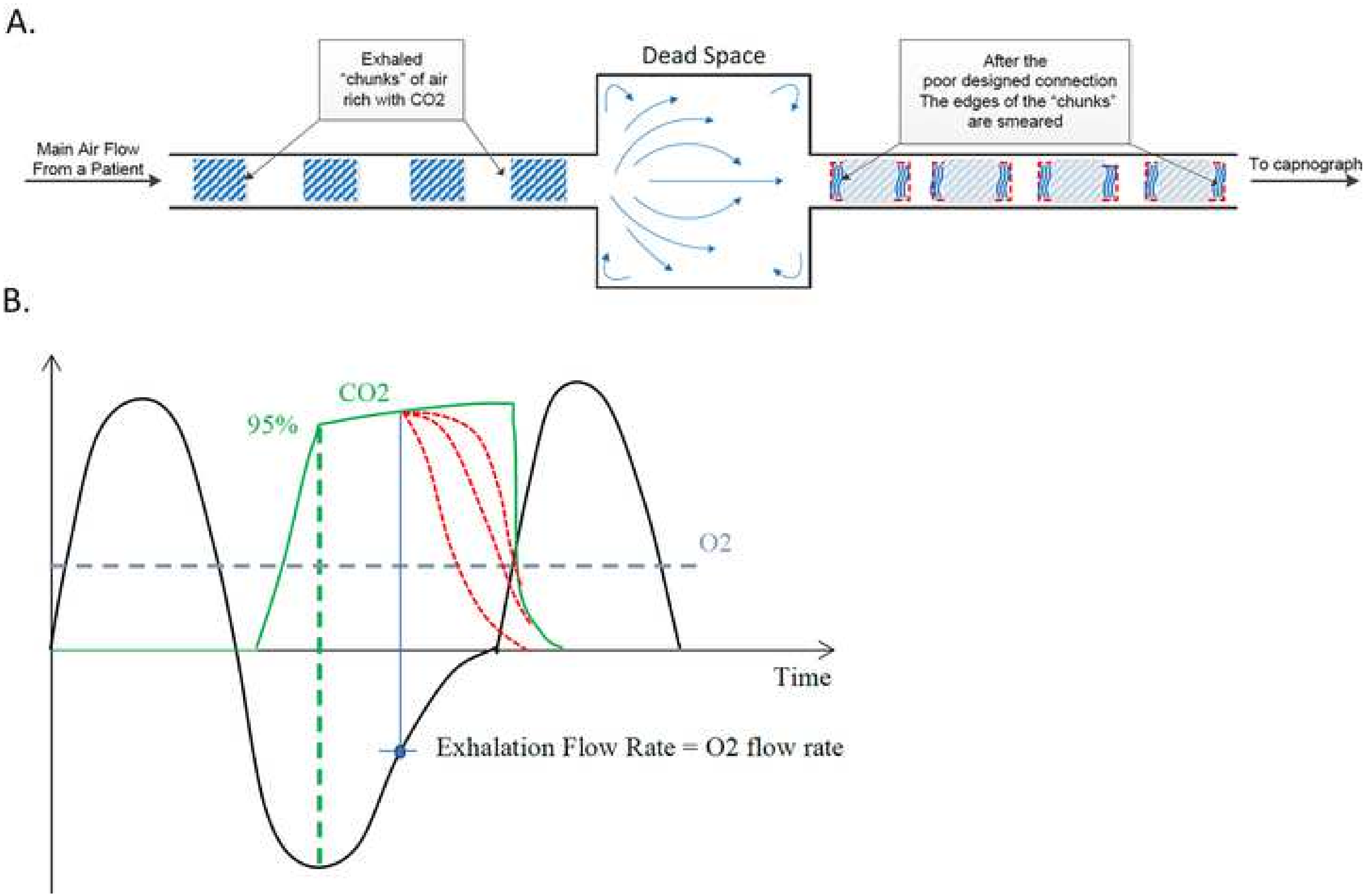
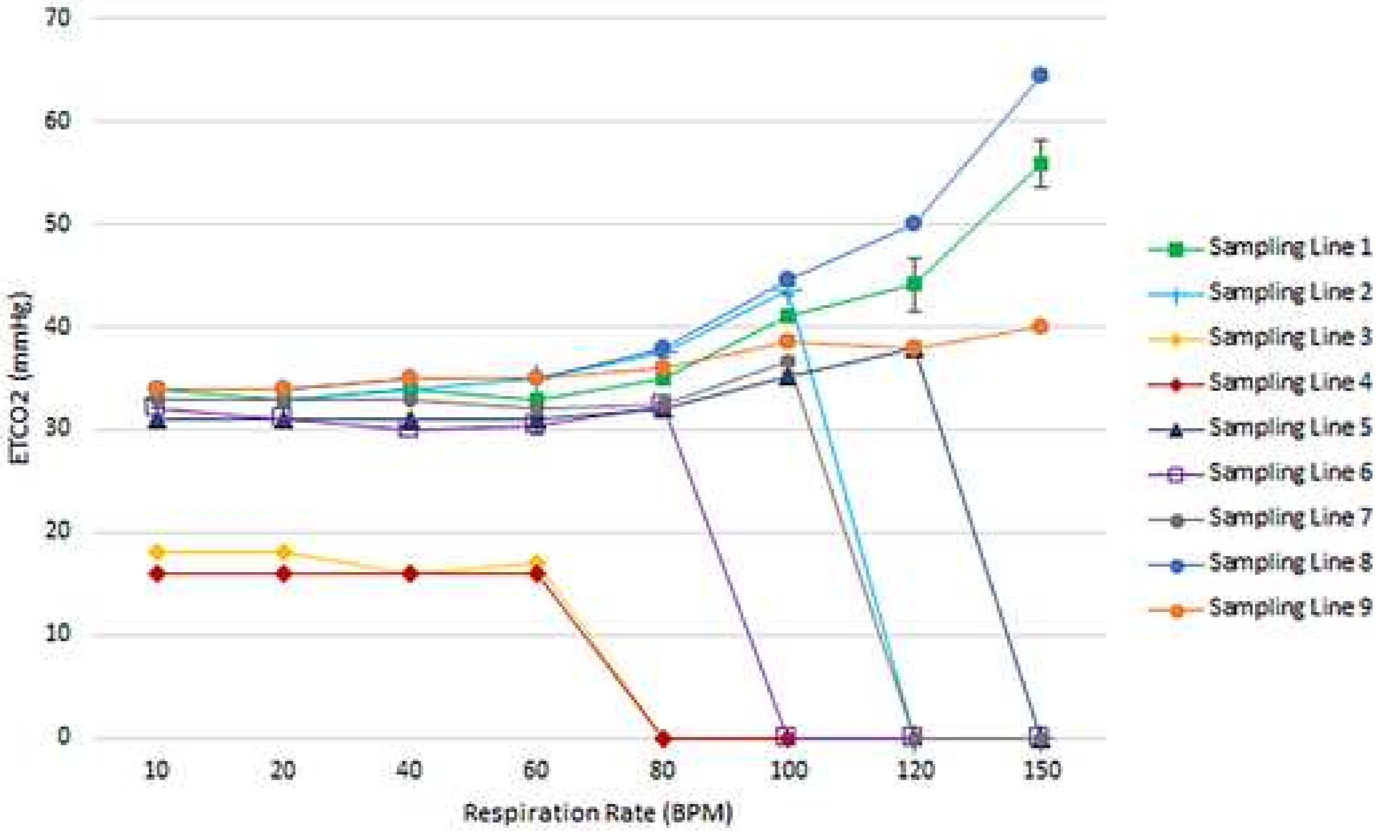

A.
Exhaled
"chunks" of air
rich with CO2
Dead Space
After the
poor designed connection
The edges of the "chunks"
are smeared
Main Air Flow
From a Patient
To capnograph
B.
CO2
95%
O2
Time
Exhalation Flow Rate = O2 flow rate

Figure 3

Figure 3

A.



B.

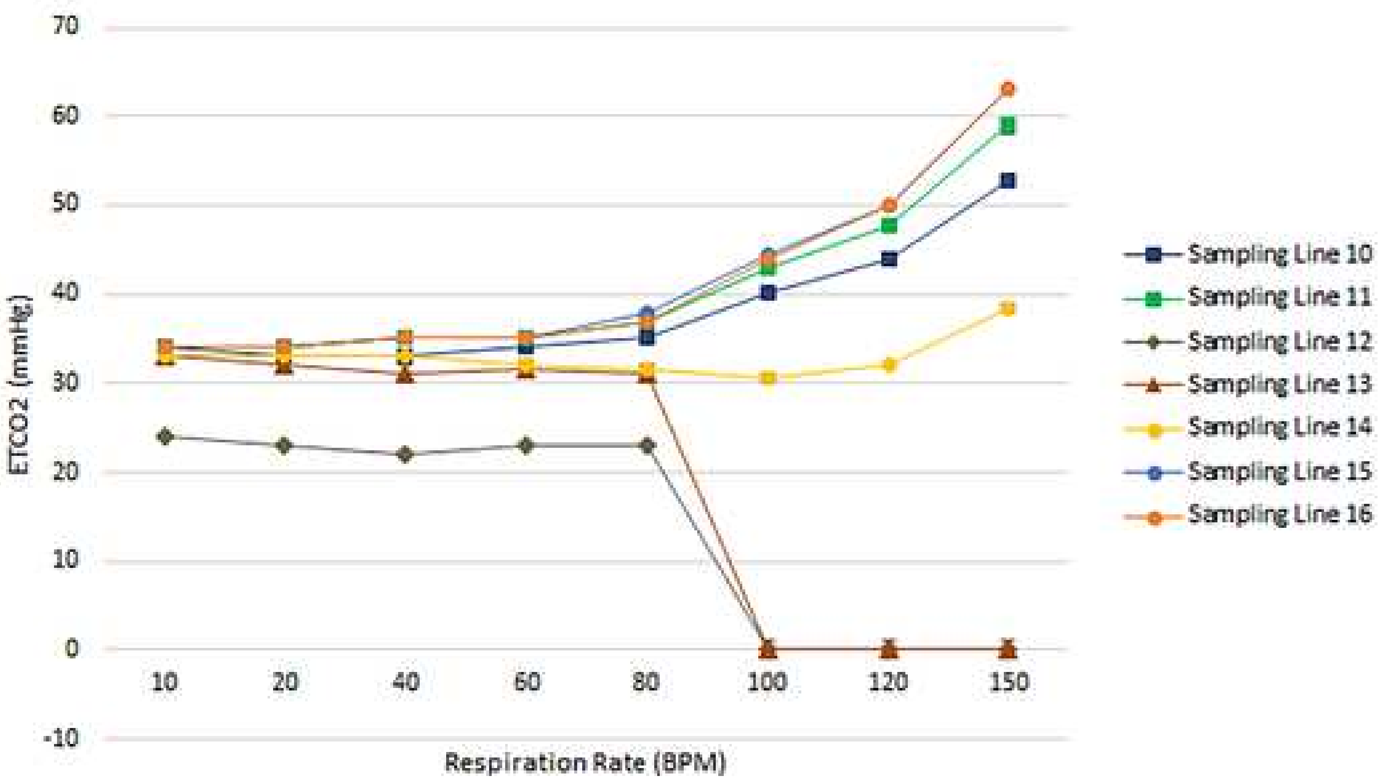


Figure 4

Figure 4

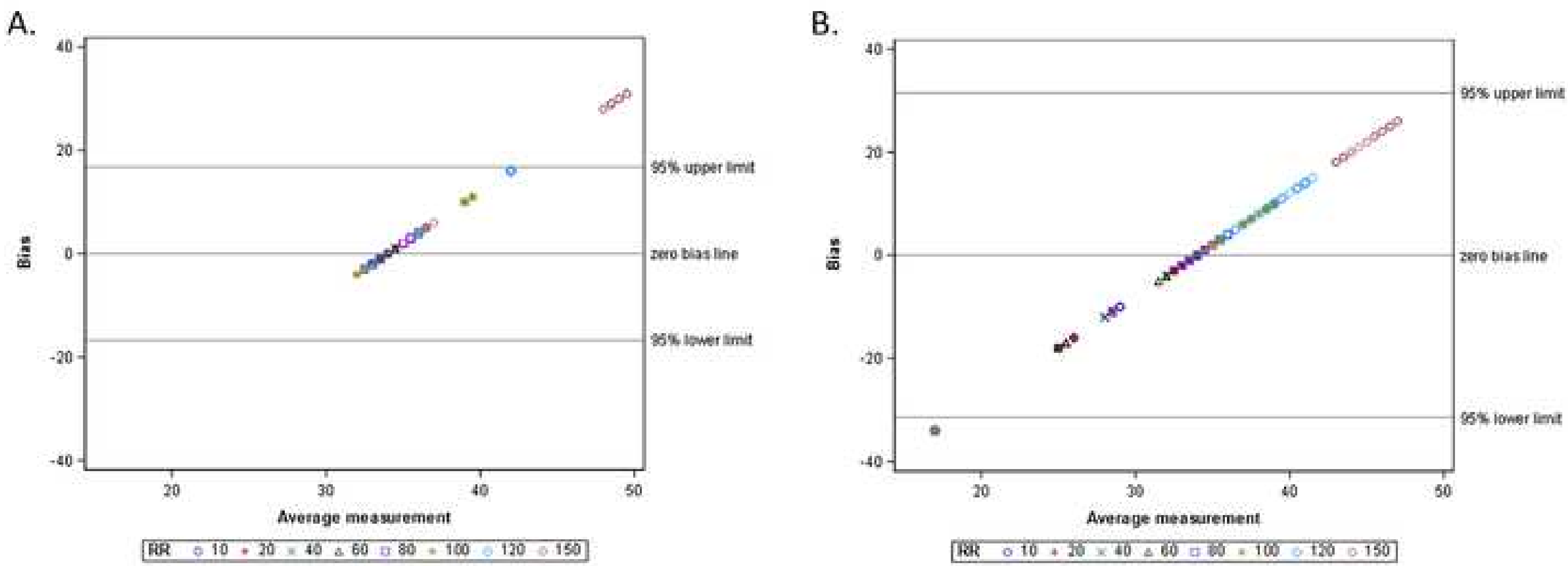


Figure 5

Click here to access/download;Figure;Fig 5.psd

Figure 5

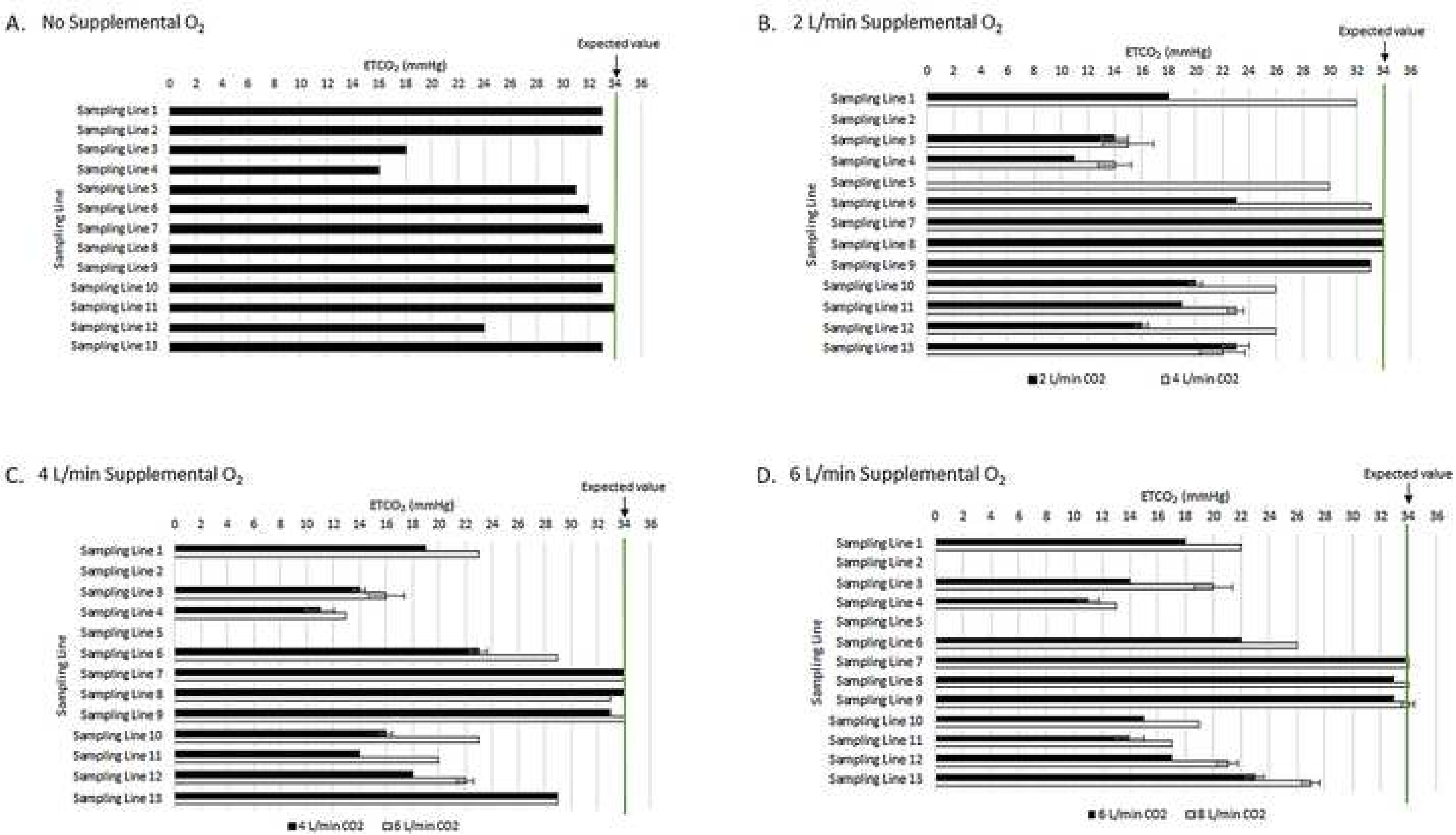
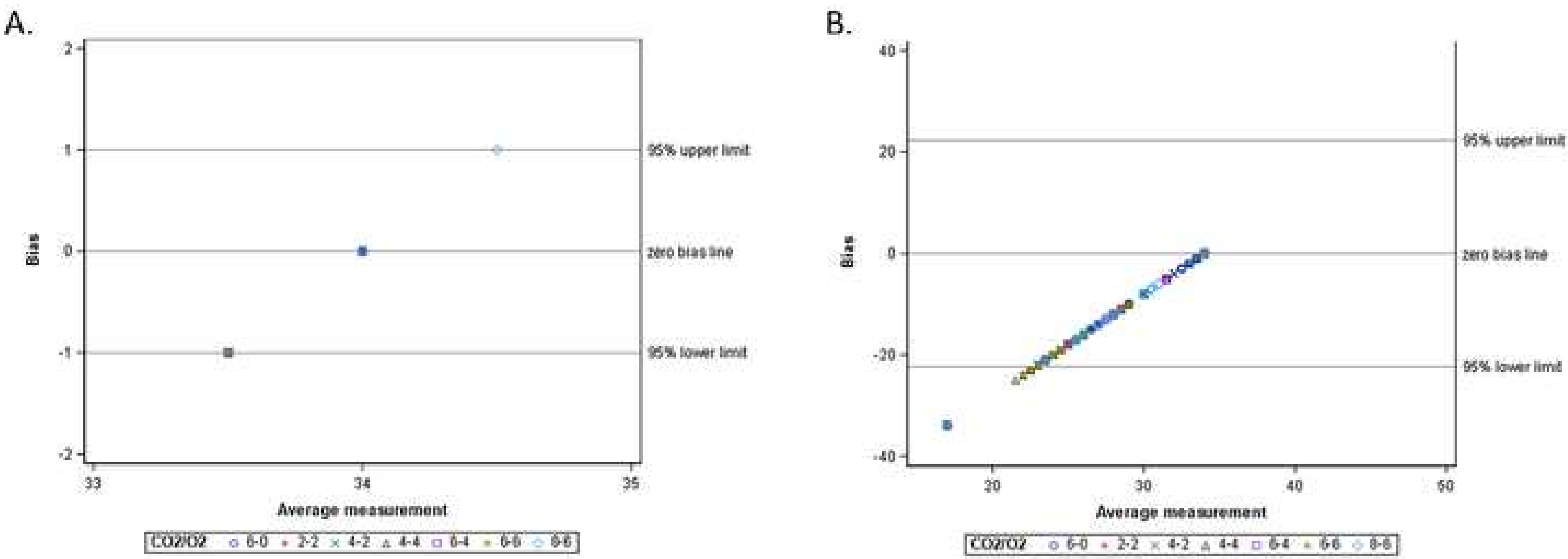


Figure 6 Click here to access/download;Figure;Fig 6.psd

Figure 6



Sampling Line Connection	O_2 connector - O_2 tube	O_2 tube- 4-way	4-way - O_2 tube	O_2 tube- cannula	Cannula - CO_2 tube
Sampling Line					
Sampling Line 1	15.68	14.78	9.94	8.81	6.16
Sampling Line 2	19.52	20.79	4.14	4.58	4.8
Sampling Line 3	10.1	11.98	5.48	4.83	7.11
Sampling Line 4	16.5	6.72	7.48	6.87	6.91
Sampling Line 5	21.87	22.88	8.81	8.61	8.62
Sampling Line 6	19.49	10.79	3.18	3.92	3.81
Sampling Line 7	24.9	18.29	12.32	8.67	7.37
Sampling Line 8	---	24.7	21.61	5.61	9.19
Sampling Line 9	21.91	19.87	6.68	7.7	5.49
Sampling Line 10	11.4	17.23	11.71	11.7	6.56
Sampling Line 11	17.88	17.7	12.86	8.2	8.58
Sampling Line 12	18.52	21.46	6.11	7.33	6.94
Sampling Line 13	12.83	15.5	6.06	6.11	6.08
Sampling Line 14	---	---	---	---	---
Sampling Line 15	26.27	22.79	5.94	8.3	11.03
Sampling Line 16	26.6	21.08	5.32	7.53	10.44

CO_2 tube - 4-way	4-way - CO_2 tube	CO_2 tube - CO_2 connector	Humidifier - tube	Tube - cannula
7.64	5.06	7.42	---	---
3.26	7.17	10.91	---	---
4.03	8.95	11.52	---	---
4.81	5.53	10.66	---	---
10.14	14.61	11.72	---	---
1.33	4.41	5.52	---	---
11.82	8.26	6.28	---	---
9.24	6.75	10.57	---	---
6.67	7.39	10.14	---	---
7.49	7.7	8.15	---	---
6.97	6.65	7.6	---	---
6.18	9.07	10.62	---	---
4.99	7.38	6.46	---	---
---	---	10.7	3.55	6.58
6.79	6.62	9.87	---	---
6.83	6.42	9.52	---	---

Sampling Line	Average Rise Time (±SD) [msec]	Maximum Respiratory Rate (*i* =1:1) [BPM]	Exhalation Time [msec] (i=1:1)	Maximum Respiratory Rate (i=1:2) [BPM]
Sampling Line 1	116 (2)	258	116.279	345
Sampling Line 2	234 (3)	128	234.375	171
Sampling Line 3	282 (8)	106	283.019	142
Sampling Line 4	186 (4)	161	186.335	216
Sampling Line 5	147 (6)	204	147.059	272
Sampling Line 6	293 (5)	102	294.118	136
Sampling Line 7	233 (3)	128	234.375	172
Sampling Line 8	122 (2)	245	122.449	327
Sampling Line 9	147 (2)	204	147.059	272
Sampling Line 10	122 (2)	245	122.449	328
Sampling Line 11	127 (2)	236	127.119	315
Sampling Line 12	264 (2)	113	265.487	152
Sampling Line 13	317 (23)	95	317	126
Sampling Line 14	123 (2)	243	123.457	326
Sampling Line 15	163 (2)	184	163.043	245
Sampling Line 16	180 (2)	166	180.723	222

Exhalation Time [msec] (i=1:2)	**Accurate after 150 BPM (*i* =1:1)**	**Accurate after 150 BPM (*i* =1:2)**
115.942	Y	Y
233.918	N	Y
281.69	N	N
185.185	Y	Y
147.059	Y	Y
294.118	N	N
232.558	N	Y
122.324	Y	Y
147.059	Y	Y
121.951	Y	Y
126.984	Y	Y
263.158	N	Y
317	N	N
122.699	Y	Y
163.265	Y	Y
180.18	Y	Y

Name of Material/ Equipment	Company	Catalog Number
Adult CO2/O2 Nasal Cannula	Respironics	M2750A
Adult Dual Nasal Cannula, Female Luer	Flexicare	032-10-126U
Divided Adult Capnograpy Cannula, Female Luer	Salter Labs	4707FTG-7-7
Divided Adult Capnograpy Cannula, Female Luer	Salter Labs	4797F-7-7
Hudson RCI Softech Bi-Flo EtCO2/O2 Cannula, Female Luer	Hudson	1845
CO2/O2 Adult Cannula, Female Luer	Westmed	539
Adult ETCO2 Cannula	Ventlab	4707
O2/CO2 Nasal FilterLine sampling line, Adult, Female Luer	Medtronic	6912
Smart CapnoLine Plus sampling line, Adult, Female Luer	Medtronic	9822
Pediatric CO2/O2 Nasal Cannula	Respironics	M2751A
Pediatric CO2/O2 Oral/Nasal Cannula	Respironics	M2761A
Divided Pediatric Capnograpy Cannula, Female Luer	Salter Labs	4703F-7-7
Hudson RCI Softech Plus Pediatric Divided Nasal Cannula	Hudson	2850
FilterLine H Set sampling line, Infant/Neonate	Medtronic	6324
O2/CO2 Nasal FilterLine sampling line, Pediatric, Female Luer	Medtronic	6913
Smart CapnoLine sampling line, Pediatric, Female Luer	Medtronic	7269
Breathing simulator	Medtronic	T-158
Capnostream 35 portable respiratory monitor	Medtronic	PM35MN
Flow/Leak Tester	Emigal Electronic test solutions LTD	N/A
Flow Meter	Omega	FMA1823A
Gas: 100% N2	Airgas	GR04930
Gas: 100% O2	Airgas	10133692
Gas: 5%CO2, 21%O2, 74% N2	Airgas	HPE400
Manikin	Tru Corp-AirSim Advance	S/N:
Rise Time Jig	Medtronic	T-547
Tensile Testing Machine	MRC Lab	B1/E
Statistical software	SAS Institute Inc	v9.4

Sampling Line Number
Sampling Line 1
Sampling Line 2
Sampling Line 3
Sampling Line 4
Sampling Line 5
Sampling Line 6
Sampling Line 7
Sampling Line 8
Sampling Line 9
Sampling Line 10
Sampling Line 11
Sampling Line 12
Sampling Line 13
Sampling Line 14
Sampling Line 15
Sampling Line 16

Comments/Description

https://www.medtronic.com/covidien/en-us/products/capnography/filterline-etco2-sampling-lines.html
https://www.medtronic.com/covidien/en-us/products/capnography/filterline-etco2-sampling-lines.html

https://www.medtronic.com/covidien/en-us/products/capnography/filterline-etco2-sampling-lines.html
https://www.medtronic.com/covidien/en-us/products/capnography/filterline-etco2-sampling-lines.html
https://www.medtronic.com/covidien/en-us/products/capnography/filterline-etco2-sampling-lines.html

https://www.medtronic.com/covidien/en-us/products/capnography/capnostream-35-portable-respiratory-monitor.html

August 02, 2020

Vineeta Bajaj, Ph.D.
Review Editor
JoVE

Re: MS#: JoVE61670R1 "Evaluation of Capnography Sampling Line Compatibility and Accuracy When Used with a Portable Capnography Monitor"

Dear Dr. Bajaj,

We would like to thank the editors and reviewers for their valuable comments on our manuscript. We herein submit a revised version of the manuscript addressing the reviewer comments, with our point-by-point responses below.

Best regards,
Ruben D. Restrepo

EDITORIAL COMMENTS

Editorial Comment 1: Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammatical errors.

Author Response: Thank you for this suggestion. We have carefully reviewed the manuscript to ensure there are no spelling or grammatical errors.

Editorial Comment 2: Protocol Language: Please ensure that ALL text in the protocol section is written in the imperative voice/tense as if you are telling someone how to do the technique (i.e. “Do this”, “Measure that” etc.) Any text that cannot be written in the imperative tense may be added as a “Note”, however, notes should be used sparingly and actions should be described in the imperative tense wherever possible.
1) Examples NOT in the imperative : 2.6.1

Author Response: We thank the editors for this comment, and have revised the protocol language to ensure all steps are written in the imperative tense, as highlighted below:

> 2.6.1 Calculate the maximum respiratory rate using the measured rise time for the sampling line and a 1:1 breath ratio, using the following equation: ~~For a 1:1 breath ratio,~~

~~the maximum respiratory rate represents the fastest allowed respiratory rate without impacting $ETCO_2$ accuracy when the time required for inhalation and exhalation are the same. This can be calculated using the measured rise time for the sampling line:~~

$$Maximum\ Respiratory\ Rate\ (BPM) = 30\,\text{sec} \div Rise\ time\ for\ sampling\ line\ (\text{sec})$$

where 30 sec represents the cumulative time used to exhale during 1 min (1:1 inhalation:exhalation time).

Note: For a 1:1 breath ratio, the maximum respiratory rate represents the fastest allowed respiratory rate without impacting $ETCO_2$ accuracy when the time required for inhalation and exhalation are the same.

2.6.2 Calculate the maximum respiratory rate using the measured rise time for the sampling line and a 1:2 breath ratio, using the following equation: ~~For a 1:2 breath ratio, the maximum respiratory rate represents the fasted allowed respiratory rate without impacting $ETCO_2$ accuracy when the time used to exhale is twice as long as the time used to inhale. This can be calculated using the measured rise time for the sampling line:~~

$$Maximum\ Respiratory\ Rate\ (BPM) = 40\,\text{sec} \div Rise\ time\ for\ sampling\ line\ (\text{sec})$$

where 40 sec represents the cumulative time used to exhale during 1 min (1:2 inhalation:exhalation time).

Note: For a 1:2 breath ratio, the maximum respiratory rate represents the fastest allowed respiratory rate without impacting $ETCO_2$ accuracy when the time used to exhale is twice as long as the time used to inhale.

In addition, we revised the protocol headings to ensure use of the proper voice:

1. **~~Measurement of~~ Measure sampling line tensile strength**
2. **Measure rise time ~~test~~ and sampling line accuracy**
3. **~~Measurement of~~ Measure $ETCO_2$ accuracy as a function of respiratory rate**
4. **~~Measurement of~~ Measure $ETCO_2$ accuracy in the presence of supplemental O_2**

Editorial Comment 3: Protocol Detail: Please note that your protocol will be used to generate the script for the video, and must contain everything that you would like shown in the video. **Please ensure that all specific details (e.g. button clicks for software actions, numerical values for settings, etc) have been added to your protocol steps.** There should be enough detail in each step to supplement the actions seen in the video so that viewers can easily replicate the protocol. Some examples:
1) 3.3.2: Mention software steps.
2) 3.3.: how?

Author Response: As requested, we have added specific details, including button clicks and numerical values for settings, to the protocol steps as outlined below:

2.1.2.5 Open the ~~LabVIEW~~ jig software and define the test parameters as follows: Air:

CO_2 ratio 1:1; Air time = 3 seconds, CO_2 time = 3 seconds, 10 cycles, rise time measurement length: none.

2.1.5 Compare the rise time value to the margins and confirm it is inside the specification limits, pre-defined as rise time background < 60 msec and rise time of a control sample, a 15 cm PVC tube, 0.95 mm internal diameter, equal to 39 ± 5 msec.

2.1.6 Compare the delivery time to the margins and confirm it is inside the specification limits, predefined as background delivery time <100 msec and delivery time of a control sample, a 15 cm PVC tube, 0.95 mm internal diameter, equal to 152 ± 5 msec.

3.3.2 ~~Using~~ Open the ~~control~~ breath simulator jig software, and ~~calibrate~~ set the ~~a~~ duty cycle to 50%.

3.3.3 Test for leaks in the system using a leak testing jig.

3.3.3.1 Connect the sampling line to the CO_2 port on the leak testing jig.

3.3.3.2 Create a kink in the sampling line to prevent CO_2 from exiting the end of the sampling line.

3.3.3.3 Using a flow rate of 50 mL/min CO_2, allow the pressure in the sampling line to increase to 300 mmHg, then stop adding CO_2.

3.3.3.4 Observe if the pressure in the sampling line remains the same or decreases. If the pressure decreases, this confirms a leak in the system, and a new sampling line should be applied in Step 3.2.

Editorial Comment 4: Protocol Highlight: Please ensure that the highlightin is under 2.75 pages (including line spaces).

Author Response: Thank you for this comment. We have removed some of the protocol highlighting to ensure that it is under 2.75 pages total.

Editorial Comment 5: Discussion: JoVE articles are focused on the methods and the protocol, thus the discussion should be similarly focused. Please ensure that the discussion covers the following in detail and in paragraph form (3-6 paragraphs): 1) modifications and troubleshooting, 2) limitations of the technique, 3) significance with respect to existing methods, 4) future applications and 5) critical steps within the protocol.

Author Response: We reviewed the discussion section to ensure that it addresses the 5 discussion topics noted above. Key portions of the discussion section, including text added to address these topics, are as follows:

1) Modifications and troubleshooting:

To apply the rise time findings to a clinical setting, we performed two tests to examine $ETCO_2$ accuracy when sampling lines were connected to a portable capnography monitor via a manikin. For both tests, we needed to modify the default capnography monitor settings to allow the monitor to recognize cross-paired sampling lines.

We needed to modify the rise time measurement parameters to remove the upper time limit on the rise time jig, so that the rise time could be collected for all sampling lines before the measurement period ended. The long rise time observed for some capnography sampling lines could reflect an increased volume of dead space in these sampling lines.

2) Limitations of the technique:

One limitation of this testing system is the continuous, gradual increase in force applied to the sampling line, as opposed to a sudden strong force, which could be encountered in clinical settings.

Although a rapid breathing rate of 150 BPM is unlikely to be encountered clinically, we determined the accuracy of each sampling device at this breath rate because it is considered the technical upper limit for many capnography sampling lines. While a respiratory rate of 150 BPM is non-physiologic, our bench test highlights that while some capnography sampling lines were accurate across the full technical range of respiratory rates, other sampling lines failed to achieve the same accuracy standard.

The main limitation of the $ETCO_2$ tests is that the tests are performed using a manikin and a controlled breathing system, as opposed to a human subject, in which breathing patterns vary between individuals.

3) Significance with respect to existing methods:

Although tensile strength tests are often performed on other types of medical devices, our method was unique in that it examined the tensile strength of each segment of the capnography sampling line. Therefore, in addition to determining ~~measuring~~ the tensile strength of each sampling line component, it also allowed for identification of the overall weak point of the complete sampling line.

…we determined the maximum respiratory rate and exhalation time for two unique breathing patterns, defined by inhalation:exhalation ratios equal to 1:1 and 1:2. This unique aspect of our analysis allowed us to evaluate the accuracy of measured CO_2 *in circumstances that represent patients whose breathing pattern is uniform or whose exhalation time lasts longer than their inhalation time.*

…similar to a previous study, we controlled respiratory rate using a respiratory rate controller, and monitored the resulting $ETCO_2$ *measurements for each sampling line.*

Importantly, many of the sampling lines failed to maintain $ETCO_2$ *accuracy upon an increase in respiratory rate or upon the introduction of supplemental* O_2*, which is consistent with previous assessments of capnography accuracy. Together, our findings are consistent with previous bench tests that successfully measure the accuracy of capnography sampling lines.*

4) Future applications:

As a validated instrument, the jig used to measure the tensile strength of the capnography sampling lines could be used for other applications, such as measuring the tensile strength of other sampling tubes and medical devices that have the potential to experience tension in a clinical setting.

Given that many of the sampling lines cross-paired to the capnography monitor exhibited reduced $ETCO_2$ *accuracy in clinically relevant circumstances, care should be taken to ensure that any cross-paired commercial sampling lines and monitors are validated before being used to monitor patient ventilation status.*

5) Critical steps within the protocol:

Although tensile strength tests are often performed on other types of medical devices, our method was unique in that it examined the tensile strength of each segment of the capnography sampling line. Therefore, in addition to determining ~~measuring~~ the tensile strength of each sampling line component, it also allowed for identification of the overall weak point of the complete sampling line.

…we determined the maximum respiratory rate and exhalation time for two unique breathing patterns, defined by inhalation:exhalation ratios equal to 1:1 and 1:2. This unique aspect of our analysis allowed us to evaluate the accuracy of measured CO_2 *in circumstances that represent patients whose breathing pattern is uniform or whose exhalation time lasts longer than their inhalation time.*

A key component of this test was the use of a pre-defined set of respiratory rates ranging from 10 to 150 BPM, to determine $ETCO_2$ accuracy across respiratory patterns that patients could exhibit.

Similar to the $ETCO_2$ accuracy test with varying respiratory rate, in this test, a key step in the protocol was to measure $ETCO_2$ accuracy across multiple supplemental oxygen flow rates.

Editorial Comment 6: Figure/Table Legends: Include a reference for Suppl File 1.

Author Response: Thank you for this comment. As requested by Reviewer 1, we have moved Supplementary Figure 1 to the main manuscript, and as such, have updated the Figure and Table Legends to reflect this. In the revised manuscript, Figure 4 (formerly Supplementary Figure 1A-B) is referenced in the results section entitled '*$ETCO_2$ accuracy as a function of respiratory rate*' and Figure 6 (formerly Supplementary Figure 1C-D) is referenced in the results section entitled '*$ETCO_2$ accuracy in the presence of supplemental oxygen*'.

Editorial Comment 7: References: Please spell out journal names.

Author Response: We have updated the references so that the full journal names are listed for each entry.

Editorial Comment 8: Commercial Language: JoVE is unable to publish manuscripts containing commercial sounding language, including trademark or registered trademark symbols (TM/R) and the mention of company brand names before an instrument or reagent. Examples of commercial sounding language in your manuscript are Nafion, compact RIO, LabVIEW, SAS (SAS Institute Inc, Medtronic, Respironics and Medtronic, (Respironics , Flexicare, Salter Labs, Hudson, Westmed, Ventlab,

1) Please use MS Word's find function (Ctrl+F), to locate and replace all commercial sounding language in your manuscript with generic names that are not company-specific. All commercial products should be sufficiently referenced in the table of materials/reagents. You may use the generic term followed by "(see table of materials)" to draw the readers' attention to specific commercial names.
2) Please remove the registered trademark symbols TM/R from the table of reagents/materials.
3) Since you are comparing various systems, we suggesting labeling them system 1, 2, 3 etc and defining the labels in the table of materials.
4) Remove all product names from all figure and tables.

Author Response: Thank you for this important comment. We have removed the following commercial language from the manuscript:

Nafion replaced with *humidifier* in all manuscript text, tables, and figures
Compact RIO replaced with *jig controller and power supply* in the manuscript text
LabVIEW replaced with *jig software* in the manuscript text
SAS replaced with *statistical software* in the manuscript text

In addition to the specific terms outlined above, we removed all commercial names for the capnography sampling lines from the manuscript text, tables, and figures, and as suggested, created a system to label the capnography sampling lines using numbers 1 through 16. These are defined by the manufacturer and product name in the Table of Materials, and the product names and manufacturers, including *Respironics, Flexicare, Salter Labs, Hudson, Westmed, Ventlab, and Medtronic*, are no longer used in the manuscript text, tables, and figures.

Finally, we have verified that registered trademark symbols are not included in the Table of Materials.

Editorial Comment 9: If your figures and tables are original and not published previously or you have already obtained figure permissions, please ignore this comment. If you are re-using figures from a previous publication, you must obtain explicit permission to re-use the figure from the previous publisher (this can be in the form of a letter from an editor or a link to the editorial policies that allows you to re-publish the figure). Please upload the text of the re-print permission (may be copied and pasted from an email/website) as a Word document to the Editorial Manager site in the "Supplemental files (as requested by JoVE)" section. Please also cite the figure appropriately in the figure legend, i.e. "This figure has been modified from [citation]."

Author Response: Our figures and tables are original and not previously published.

REVIEWER 1

This is well written manuscript and performed a good comparisons among several sampling tube. They considered the tensile strength, rise time, $ETCO_2$ accuracy as a function of respiratory rate, and $ETCO_2$ accuracy in the presence of supplemental O_2 as assessment parameters for several sampling tube. The method is well written and explained. The finding of this research is analysed used well established method namely, Bland Altman plot.

Reviewer 1, Comment 1: Line 509; Together, these tests suggest that devices with a longer rise time have a lower maximum accurate respiration rate and exhibit low $ETCO_2$ accuracy at the maximum accurate respiration rate.

Do you want to say that the bad performance of other sampling tube rather than medtronic, happened due to longer rise time, hence it depends upon the CO_2 sensor response time, having lower rise time, may provide similar results.

Author Response: We thank the reviewer for this question regarding the relationship between rise time and sensor response time. Importantly, the CO_2 sensor response time equals the total of (1) the rise time of the sampling line and (2) the delay time, defined as the time required for the monitor to calculate $ETCO_2$. Since the same capnography monitor was used for all bench tests, the delay time is equal across all 16 capnography sampling lines reported. Therefore, the performance of the sampling lines does not require consideration of the CO_2 sensor response time (a constant value), but instead can be compared by the rise time alone.

Reviewer 1, Comment 2: As, relatively high sampling rate (i.e. 150 ml-min-l), may reduce the response time which indirectly reflect on rise time, may provide a better way to compare the sampling tube, I mean, the sampling tube which does perform well on higher sampling rate, may have similar results. The experiment should be performed with higher sampling flow rate to see the impact of rise time.

Author Response: We appreciate the reviewer's suggestion to perform the experiment with a higher sampling flow rate. Importantly, the rise time experiment was performed with the capnography monitor set at its maximum sampling flow rate, which is 50 mL/min. Therefore, we did not perform the experiment again with a higher sampling flow rate than originally used. However, we did add this important detail to the Protocol section as follows:

> *2.1.2.4 Calibrate the air and CO_2 flow to 10 L/min and the gas sampling rate to 50 mL/min using a mass flow meter and a dedicated restrictor. Note: The maximum sampling rate of the capnography monitor is 50 mL/min.*

Reviewer 1, Comment 3: I am curious to see the result of Bland altman plot with 95% confidence interval with upper and lower limit from its mean value, rather than bar graph.

Author Response: Thank you for this comment. Our initial manuscript submission included a supplementary figure of Bland Altman plots, displaying the bias with 95% confidence intervals for both $ETCO_2$ bench tests. Importantly, our revised manuscript includes these plots as Figures 4 and 6, for $ETCO_2$ accuracy as a function of respiratory rate and $ETCO_2$ accuracy in the presence of supplemental O_2, respectively. We hope that moving these plots to the main manuscript will avoid them potentially being missed by readers. The figure legends are now as follows:

> ***Figure 4: Bland-Altman plot for $ETCO_2$ measures by (A)*** *Matched sampling lines as a function of increasing respiratory rate and* ***(B)*** *Cross-paired sampling lines as a function of increasing respiratory rate.*

__Figure 6: Bland-Altman plot for $ETCO_2$ measures by__ (__A__) Matched sampling lines as a function of increasing supplemental O_2 flow rate; (__B__) Cross-paired sampling lines as a function of increasing supplemental O_2 flow rate.

<u>Reviewer 1, Comment 4</u>: The sampling tube utilized from Medtronic are five that is comparatively more than the other company, which may provide bias results.

<u>Author Response:</u> We thank the reviewer for this important comment. As explained in the revised manuscript, we compared the bench test results between sampling lines from the same manufacturer as the capnography monitor (Medtronic, labeled in the manuscript as 'matched' sampling lines) vs sampling lines from alternate manufacturers (labeled in the manuscript as 'cross-paired' sampling lines). Since the key comparison was the performance of matched vs cross-paired sampling lines, we felt it necessary to include more than 1 matched sampling line across the bench tests, so that the results are not biased by a single matched sampling line. In addition, since the capnography sampling line designs vary by manufacturer, including multiple styles of matched Medtronic sampling lines allows for a more equal comparison against the varied designs tested from other manufacturers. In this way, we ensured an 'apples to apples' comparison, as opposed to an 'apples to oranges' comparison among the designs of the matched and cross-paired sampling lines. For these reasons, we have opted to retain the comparisons as in the originally submitted manuscript, and we added the following text at the beginning of the Protocol to clarify the comparison between matched and cross-paired sampling lines:

> *The capnography sampling lines used in these bench tests included 16 adult, pediatric, and neonatal capnography sampling lines from 7 commercial sources. Among the 16 sampling lines included in the bench tests, 5 sampling lines were from the same manufacturer as the capnography monitor utilized for the bench tests ('matched'), and 11 sampling lines were from alternate manufacturers ('cross-paired') (Table of Materials).*

<u>Reviewer 1, Comment 5</u>: The balnd altman analaysis should provide the in main text rather than in supplementary.

<u>Author Response</u>: As suggested by the reviewer, we have moved the Bland Altman plots to the main manuscript, where they are reported in the revised manuscript as Figures 4 and 6. The figure legends are now as follows:

__Figure 4: Bland-Altman plot for $ETCO_2$ measures by__ (__A__) Matched sampling lines as a function of increasing respiratory rate and __(B)__ Cross-paired sampling lines as a function of increasing respiratory rate.

Figure 6: Bland-Altman plot for $ETCO_2$ measures by (A) Matched sampling lines as a function of increasing supplemental O_2 flow rate; (B) Cross-paired sampling lines as a function of increasing supplemental O_2 flow rate.

Reviewer 1, Comment 6: What is reference rise time (60 msec) ? if I am not wrong line (205) Record the background rise time and ensure the result is less than 60 msec. There are the sensor having lower response time comet, Sprint IR.

Author Response: The reviewer is correct that the background rise time, measured during calibration, is <60 msec. In addition, the rise time using a control sample, defined as a 15 cm PVC tube, 0.95 mm internal diameter, is expected to be 39 ± 5msec. Although not previously defined in the manuscript, the acceptable background delivery time is defined as <100 msec, with delivery time of a control sample (15cm PVC tube, 0.95 mm internal diameter) equal to 152 ± 5 msec. We have added these details to the Protocol section of the manuscript as below:

> *2.1.5 Compare the rise time value to the margins and confirm it is inside the specification limits, pre-defined as rise time background < 60 msec and rise time of a control sample, a 15 cm PVC tube, 0.95 mm internal diameter, equal to 39 ± 5 msec.*
>
> *2.1.6 Compare the delivery time to the margins and confirm it is inside the specification limits, predefined as background delivery time <100 msec and delivery time of a control sample, a 15 cm PVC tube, 0.95 mm internal diameter, equal to 152 ± 5 msec.*

Importantly, while other capnography monitors, such as the Sprint IR sensor mentioned by the reviewer may have a different response time, the purpose of our bench tests was to compare capnography sampling lines to one another using a single type of capnography monitor. Exploration of performance differences between multiple capnography monitors was out of the scope of this analysis, but is certainly a valuable topic for future studies.

REVIEWER 2

Reviewer 2, Comment 1: There are two different technologies for clinical capnography and two very different uses of clinical capnography. Types of capnography include in-line version and the side-stream version, capnography for breathing circuits in intubated patients and capnography for non-intubated patients using a nasal cannula. To bring clarity to this while concurrently orienting the reader to this being a study specifically on "nasal cannula capnography" would really help those who heavily use capnography hone in on what this particular study is focusing on while at the same time educating those who aren't as experienced on the diversity of types and uses of capnography. I do note that the last sentence of the introduction describes capnography as being used in intubated patients, but it does not bring clarity to the fact that intubated patients can use in-line or side-stream and that this is a differently designed sample line.

Author Response: This is an excellent comment. As the reviewer notes, we initially provided little background on mainstream vs sidestream capnography, and have revised the introduction to include clarification that this study was focused on sidestream capnography, to compare performance of nasal cannula sampling lines. Key modifications to the Introduction section are as follows:

> *Inherent in the use of capnography is reliance on a device that provides the clinician with an accurate assessment of a patient's ventilatory status. Capnography monitoring can be either sidestream, in which exhaled breath is diverted to a monitor by a nasal cannula and tubing, or mainstream, in which exhaled breath is measured at the source without diverting the sample. Mainstream capnography is most often used in intubated patients, whereas sidestream capnography is used for both intubated and non-intubated patients. One important component of sidestream capnography is the sampling line…*
>
> *For example, nasal cannula sampling lines can have up to 10 connections between the nasal cannula, humidifier, $ETCO_2$ sampling line, and O_2 delivery tubes (Figure 1).*
>
> *The performance of nasal cannula sampling lines can be evaluated by a variety of tests such as the overall weak point and rise time.*
>
> *Another critical element of sidestream capnography monitoring affected by sampling line design is rise time…*
>
> *The purpose of this study was to determine the compatibility and accuracy of commercially available sidestream capnography sampling lines used in conjunction with a portable capnography monitor.*

Reviewer 2, Comment 2: As the text of the article develops it seems to evolve into a comparison of Medtronic sample lines vs non-Medtronic sample lines. Considering that the authors all have Medtronic connections it would be in order to clarify "the reason" for separating out the Medtronic lines. Ironically it would both allow more description regarding the superior performance of the Medtronic lines while also giving a reason for the Medtronic vs non-Medtronic grouping, which currently has the appearance of being associated with corporate bias. I think that this issue can be clarified because there does seem to be a qualitative difference between the Medtronic and non-Medtronic sample lines. If there is no result related basis for grouping Medtronic vs non-Medtronic then it would be better not describe this group comparison. This is a major issue with the paper that should be addressed.

Author Response: We thank the reviewer for highlighting this topic, which was also raised by Reviewer 1. As explained in the revised manuscript, we compared the bench test results between sampling lines from the same manufacturer as the capnography monitor (Medtronic, labeled in the manuscript as 'matched' sampling lines) vs sampling lines from alternate manufacturers (labeled in the manuscript as 'cross-paired' sampling lines). By re-defining these groups of sampling lines into matched vs cross-paired groups, as opposed to Medtronic vs non-Medtronic, the emphasis of our observations is on the qualitative difference between these groups of sampling lines, and less on the manufacturer, avoiding potential corporate bias. In addition, we consider the matched Medtronic sampling lines to be an appropriate control group for comparison against the cross-paired sampling lines' performance with a Medtronic capnography monitor, and as mentioned in our response to Reviewer 1, Comment 4, we included multiple styles of matched sampling lines to allow for a more equal comparison against the varied sampling line designs tested from other manufacturers.

Among many manuscript modifications to remove references to specific sampling line manufacturers, we added the following text at the beginning of the Protocol to clarify the comparison between matched and cross-paired sampling lines:

> *The capnography sampling lines used in these bench tests included 16 adult, pediatric, and neonatal capnography sampling lines from 7 commercial sources. Among the 16 sampling lines included in the bench tests, 5 sampling lines were from the same manufacturer as the capnography monitor utilized for the bench tests ('matched'), and 11 sampling lines were from alternate manufacturers ('cross-paired') (Table of Materials).*

Reviewer 2, Comment 3: Why were the various respiratory rate points chosen? Why is it important or significant that a sample line performs at a respiratory rate of 150 breaths per minute? As a clinician I can't imagine a person, even a neonate breathing at 150 BPM and just need to understand why performance at this level significant or why this rate was chosen. It would be important to mention that the high respiratory rates are non-physiologic, but that some of the lines performed so well that they could function with these non-physiologic rates.

Author Response: This is an excellent question. We chose a variety of respiratory rates to reflect possible breathing scenarios encountered in clinical settings. Importantly, we included up to 150 BPM because this respiratory rate is defined as the technical upper limit for many capnography sampling lines. Thus, even if a respiratory rate of 150 BPM is unlikely to occur in a clinical setting, as a bench test, we felt it was appropriate to test the full technical range of the devices. We have added this detail to the Discussion section as reflected below:

> *Although a rapid breathing rate of 150 BPM is unlikely to be encountered clinically, we determined the accuracy of each sampling device at this high breath rate because it is considered the technical upper limit for many capnography sampling lines. While a*

respiratory rate of 150 BPM is non-physiologic, our bench test highlights that while some capnography sampling lines were accurate across the full technical range of respiratory rates, other sampling lines failed to achieve the same accuracy standard.

Reviewer 2, Comment 4: Figure 3A is without proper captioning. The reader has to go back to the text of the article to understand that all of the lines were tested with a CO_2 level of 34mmHg. What is not clear and not addressed is why the sample lines were reading higher and much higher CO_2 levels than 34 mmHg per this graph. The issue of captioning applies to all of the figures.

Author Response: Based on the reviewer's comment, we have added the following detail to the figure legend for Figure 3:

Figure 3: $ETCO_2$ accuracy of adult and pediatric capnography sampling lines as a function of respiration rate. Measured $ETCO_2$ values for (A) Adult and (B) Pediatric and Neonatal capnography sampling lines across a range of respiratory rates from 10 to 150 BPM. In all cases, the expected $ETCO_2$ value is 34 mmHg.

Please note that the expected $ETCO_2$ value of 34 mmHg was already highlighted in the Figure 5 legend:

Figure 5: $ETCO_2$ accuracy of capnography sampling lines in the presence of increasing supplemental oxygen. $ETCO_2$ accuracy is reported for (A) No supplemental oxygen; (B) 2 L/min supplemental oxygen; (C) 4 L/min supplemental oxygen; and (D) 6 L/min supplemental oxygen. The green line at 34 mmHg represents the expected $ETCO_2$ value across all measurements.

With respect to the sampling lines that read $ETCO_2$ levels higher than 34 mmHg at higher respiration rates, this is partially addressed in the Results section, in which we pre-defined the acceptable accuracy for readings between 0-38 mmHg and readings >38 mmHg:

The expected $ETCO_2$ in the presence of 5% CO_2 was 34 mmHg at ambient pressure, and the range predefined as acceptable accuracy was ±2 mmHg for readings between 0-38 mmHg and ±5% of the reading + 0.08 for every 1 mmHg above 38 mmHg.

The high $ETCO_2$ readings are likely due to the sampling line design and the amount of dead space present within the sampling lines, where less dead space may result in increased $ETCO_2$ measurements, and more dead space within the sampling line leads to mixed breath samples (Figure 2A). In the case of a large volume of dead space, the amplitude of the mixed breath becomes so low that the capnography monitor does not recognize it as a valid breath (Figure 2B). While this concept was addressed in the Discussion section, we have added more detail to address the topic:

This accuracy could be due to the design of the sampling lines, such that those with higher friction or larger dead space volume result in lower resolution breath samples at increased respiratory rate, similar to what we observed in the rise time test. While the sampling lines with high $ETCO_2$ readings may contain less dead space that enable them to deliver discrete breath samples, the error of $ETCO_2$ readings above 38 mmHg was pre-defined as ±5% of the reading + 0.08 for every 1 mmHg above 38 mmHg. This could partially explain why the $ETCO_2$ readings were increased above 34 mmHg during high respiratory rate in some sampling lines. In contrast, the sampling lines with low or zero $ETCO_2$ readings may contain more dead space, resulting in mixed breath samples that the capnography monitor does not recognize as valid breaths, and thus reports as no breath.

Reviewer 2, Comment 5: I as a reader have a perception that the "breathing jig" design may be important. Unfortunately I don't understand how this jig is set up, how the breaths were simulated and whether its design may have impacted sample line performance. Considering the fact that some of the sample lines had unbelievably poor performance (0 breaths detected when oxygen was flowing), why people would be purchasing a useless sample line, unless the clinical performance on actual humans was different. Thus I wonder about the realism of the "breathing jig".

Author Response: We thank the reviewer for this question. With respect to the breathing jig, we have added a more detailed description of the jig to the Protocol section of the manuscript:

3.3 Prepare and calibrate the breath simulator jig, to control the simulated respiratory rate. Note: The breath simulator jig is composed of a 2-way electrical operating valve, allowing for precise control of the flow of CO_2 and N_2 to the manikin, to simulate human breathing.

Although we do not speculate in the manuscript on the reason why poor-accuracy sampling lines are purchased, it is important to highlight potential reasons for the poor accuracy observed in our bench tests. The breathing jig is simply used to control the amount of CO_2 'exhaled' by the manikin, to represent a human breath. While this bench test may not perfectly reflect the real breath patterns of humans, it is designed as a controlled system to mimic breathing. We highlighted this as a limitation in the Discussion section:

The main limitation of the $ETCO_2$ tests is that the tests are performed using a manikin and a controlled breathing system, as opposed to a human subject, in which breathing patterns vary between individuals.

Our interpretation of the poor performance of some capnography sampling lines in the presence of supplemental O_2 is that this is not an experimental artifact, but rather, a reflection of the capnography sampling line design. In particular, most of the dead space within a sampling line is within the cannula, which delivers oxygen to the patient and collects exhaled breath for $ETCO_2$ measurement. If the sampling line is designed with a large dead space in the cannula, during oxygen delivery, the O_2 can become mixed with the exhaled breath, resulting in dilution of the exhaled breath and a low amplitude $ETCO_2$ curve that the capnography monitor does not detect as a valid breath. Therefore, if the sampling line, and in particular, the nasal cannula, is not carefully designed, in the presence of higher flow oxygen, $ETCO_2$ cannot be accurately measured by the capnography sampling line and monitor. We have added this to the discussion as below:

> *In particular, similar to our observations upon increase of the respiratory rate, the $ETCO_2$ readings for sampling lines 2 and 5 dropped to 0 mmHg in the presence of supplemental O_2, suggesting that their $ETCO_2$ accuracy when cross-paired with a capnography monitor is very low. This may be due to the design of the sampling lines, and in particular, the nasal cannula design, which is designed to both deliver oxygen to a patient and collect breath samples from a patient. If the nasal cannula contains a large amount of dead space, mixing of the supplemental oxygen and the exhaled breath can occur, resulting in low amplitude, mixed breaths that the capnography monitor does not detect as exhaled breath. In such a case, the $ETCO_2$ measurement would drop to zero, as we observed with some of the cross-paired sampling lines tested.*

We thank the reviewers for the time and effort they have devoted to critically reviewing our manuscript. The reviewer's comments are much appreciated and we hope the changes made in response to their recommendations have strengthened the manuscript for publication in *JoVE*.

Please feel free to contact me with any questions.

Kind regards,

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