Side Stream End-Tidal CO_2 Monitoring in Subjects Undergoing Non-Invasive Ventilation for Respiratory Failure: A Pilot Study

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Abstract: *Purpose:* End-tidal CO_2 (P_{ETCO2}) is an important value to guide ventilation. For non-invasive ventilation (NIV) this is not always possible due to low flows. The Capnostream® monitor is able to measure P_{ETCO2} in low flows. In this study the value of low flow P_{ETCO2} measurement during non-invasive ventilation (NIV) will be assessed. A dimensionless number, provided by the Capnostream® monitor, to reflect respiration quality: the Integrated Pulmonary Index™ is also assessed.

Methods: Subjects undergoing NIV were included. Repetitive P_aCO_2 values were matched with P_{ETCO2} values in time. Correlation was assessed using Pearson's R and Bland-Altman plots. IPI™ was recorded over time and analysed for trends over time.

Results: Correlation between P_{ETCO2} and P_aCO_2 was moderate to good. In the total group Pearson's R was 0.75 ($p < 0.001$), for subjects with COPD 0.86 ($p < 0.001$) and for subjects without COPD 0.89 ($p < 0.001$). However, Bland-Altman plots show that the limits of agreement exceeded the predetermined acceptable variation. IPI™ analysis was hampered by large proportions of missing data. IPI™ was higher in non-COPD subjects and in subjects improving during ventilation. However, neither an incline was seen over time in subjects improving nor a decline in subjects deteriorating, while on NIV.

Conclusion: Correlation between side-stream P_{ETCO2} and P_aCO_2 was moderate to good, but showed a wide variation in Bland-Altman analysis and is therefore of only modest value in clinical practice. IPI™ analysis was hampered by missing data and did not have an additive value in standard clinical care.

Keywords: Non-invasive ventilation, end tidal CO_2, P_aCO_2, blood gas analysis, capnography.

1. INTRODUCTION

Measurement of carbon dioxide (CO_2) is an established part of the monitoring of mechanically ventilated subjects. In the expiratory flow, the so called end-tidal CO_2 (P_{ETCO2}) is measured and generally correlates well with the partial pressure of arterial carbon dioxide (P_aCO_2). It is an essential parameter in mechanical ventilated subjects to evaluate and guide treatment. This correlation is less reliable when a plateau phase is not reached, as in severe chronic obstructive pulmonary diseases (COPD) or other bronchospastic disease, or when a considerable ventilation/perfusion (V/Q) mismatch is present, e.g. lung emphysema, ARDS and pulmonary embolism. In these circumstances, the measured P_{ETCO2} will be an underestimation of the P_aCO_2. To analyze the carbon dioxide content in the expiratory flow, a minimal gas flow is necessary. In intubated subjects, this can be done reliably and is used routinely in standard care. In non-intubated subjects minimal required gas flow was a limiting factor in measuring P_{ETCO2}. For those subjects frequent arterial blood gas measurement were used for CO_2 monitoring.

In recent years several techniques have been developed to measure P_{ETCO2} when only a small gas flow is present. Goldman [1] was the first to describe a method of P_{ETCO2} measurement *via* a nasal cannula in 1988. In 1989 Bowe *et al*. [2] presented a self-made, reliable technique for P_{ETCO2} measurement *via* a nasal cannula. In subjects scheduled for surgery, no significant differences were found in measured P_{ETCO2} values, comparing pre-intubation nasal cannulae with post-intubation measurements. Lenz *et al,* [3] analyzed the correlation of P_aCO_2 and P_{ETCO2} *via* side stream measurement in subjects after major surgery and found that mean values of P_aCO_2 and P_{ETCO2} were comparable, but in individual measurements large differences were noticed. Nonetheless, these differences remained almost stable during various measurements, so a trend in P_aCO_2 could be monitored using P_{ETCO2}. In 1994 Barton and colleagues investigated the correlation of P_aCO_2 and P_{ETCO2} in non-intubated Emergency Department patients [4]. An acceptable correlation was found, although P_{ETCO2} was consistently lower than P_aCO_2. This finding was also observed by Casati *et al*. [5]. Side stream CO_2

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measurements have been investigated in (intubated) neonates [6, 7], subjects in the Emergency Department [5], subjects undergoing ambulatory procedures [8] and postoperative subjects [9]. Studies have shown that side-stream P_{ETCO2} measurements are reliable in obese subjects, with or without obstructive sleep apnea syndrome [9]. Furthermore, Nuccio *et al*. [10] and Taft *et al*. [11] proved that side-stream P_{ETCO2} measurements could be used in healthy non-invasive ventilated persons in sleep laboratories.

Despite these promising results in side-stream P_{ETCO2} monitoring in non-ventilated subjects and healthy non-invasive ventilated subjects, to date no publications are available about non-invasive ventilated subjects, e.g. suffering from COPD. In this group of subjects a reliable measurement of P_{ETCO2} would mean a continuous P_{CO2} monitoring and less need for arterial blood sampling, which offers a possibility for direct treatment. However, correlation and reliability in subjects with pulmonary pathology has not yet been clearly investigated [12, 13].

To study the value of side stream end-tidal CO_2 monitoring in subjects undergoing non-invasive ventilation (NIV) for respiratory failure, we designed a pilot study to assess the value of side-stream P_{ETCO2}. We differentiate between COPD and non-COPD subjects because of the limitations of P_{ETCO2} monitoring in COPD subjects as mentioned before. As a second endpoint, we assessed the value of the Integrated Pulmonary Index™ (IPI™) [11] (Oridion® Medical 1987 Ltd., Jerusalem, Israel) in subjects undergoing NIV for respiratory failure. The IPI™ is calculated from side-stream P_{ETCO2}, respiration rate, heart rate and oxygen saturation (S_pO_2). This Integrated Pulmonary Index™, with patented algorithm, is a score from 0 to 10 that reflects quality of respiration and detects deterioration over time by worsening of the score. Scores of 8-10 are considered to be good, whereas in scores 5-7 it is recommended to monitor the subject more closely. In scores 1-4 intervention is advised [11]. It has been developed to simplify monitoring of subjects who are at risk of insufficient respiratory function and has proven useful in Post Anesthesia Care Units (PACU) [14] and during procedural sedation [15]. However, this score has not been used and validated in critically ill subjects undergoing non-invasive mechanical ventilation.

2. METHODS

2.1. Study Design

The study design was a prospective observational pilot study. Subject inclusion was planned from March 2012 till December 2012.

2.2. Study Population

The inclusion criteria were the clinical need for non-invasive ventilation as judged by the attending clinician and informed consent. At baseline, no exclusion criteria were formulated, but in case of NIV leakage due to the nasal canulla, and hence producing incorrect measurements, subjects were excluded. All subjects were admitted to our 17-bedded mixed ICU in a large teaching hospital (Gelderse Vallei Hospital, Ede, the Netherlands). The study was approved by the medical ethical board of the hospital and consent was obtained from the subjects or their relatives. Subjects were ventilated by either the BiPAP Vision (Philips®/ Respironics®) or with the NIV function of the Servo-I ventilator (Maquet®), using a full face mask.

2.3. Data Collection

From the subjects who gave informed consent the following characteristics were recorded at admission: reason of admission, age, sex, APACHE II and IV score, pulmonary history, cardiac history, relevant medical history and the use of medication. On the ICU the following parameters were recorded using our patient data management system Metavision (iMD*soft* Inc., Needham, MA, USA): non-invasive ventilation (NIV) parameters, respiratory rate, blood pressure, heart rhythm and rate, and temperature. According to the local NIV protocol we performed blood gas measurements at initiation of NIV, 30–60 minutes later and thereafter every 6 hours, or whenever needed based on clinical judgment. We used the Capno-stream20 monitor with Microstream® Capnography technology (Oridion® Medical 1987 Ltd., Jerusalem, Israel) together with 'Microstream® Smart Capnoline® Plus O_2' tubing, to record the end-tidal CO_2 (P_{ETCO2}) and the Integrated Pulmonary Index (IPI™). These parameters were recorded every 5 seconds.

P_{ETCO2} and P_aCO_2 data were matched in time by registration of the exact time of collection of blood on the Capnostream20® monitor. The P_{ETCO2} value could be read from the saved data-tables. When exact time of blood collection was not recorded on the monitor, the time shown in the laboratory results was used to match with the P_{ETCO2} value.

Data for IPI™ were recorded every 5 seconds by the Capnostream® monitor. Since we studied a trend in IPI™, we used data with an interval of 15 minutes for our analysis. Since deterioration or improvement will be most evident in the last few hours of monitoring we analyzed IPI™ in the 6 hours before cessation of NIV,

intubation or death of a subject. If the parameters for IPI™ were not reliable (e.g. due to disconnection or interference), the nearest reliable value in time was used. If no reliable value was found within 3 minutes before or after the exact time-point, it was scored as 'not available'.

2.4. Statistical Analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics 21®), as well as Microsoft Excel 2010® with added Analysis Toolpak. A p-value less than 0.05 was considered significant. To assess correlation a correlation coefficient plot was made and a Pearson's R with p-value was calculated for the total population. Since P_aCO_2 is the gold standard in CO_2 measurements, a Pearson's R greater than 0.90 was considered as good correlation. To assess agreement a Bland-Altman plot [16] was made. In the original Bland-Altman plot the difference of the measurements is plotted against the mean of these measurements. However, since we are using the gold standard, we adopted the modified Bland-Altman plot of Krouwer *et al*. [17], whereby the difference between measurements is plotted against this gold standard.

Difference between P_aCO_2 and P_{ETCO2} ($P_{(a\text{-}et)}CO_2$) in intubated subjects without significant pulmonary pathology is reported to be about 4 - 5mmHg, reflecting dead space ventilation. Lujan *et al*. [18] performed a study to assess the $P_{(a\text{-}et)}CO_2$ in COPD subjects. Arterial blood gas measurements were compared to P_{ETCO2} values obtained by side-stream capnography through a mouthpiece. $P_{(a\text{-}et)}CO_2$ ranged from 1.7 ± 2.9mmHg in healthy subjects to 8.2 ± 5.6mmHg in COPD subjects. In studies investigating the *nasal* P_{ETCO2} in several settings, a $P_{(a\text{-}et)}CO_2$ of about 0.6 - 1.0kPa (4.3-7.5mmHg0 was found [5, 8, 9]. Therefore, good agreement for this study was defined as a difference of ≤ 7.5mmHg and limits of agreement maximally 4mmHg.

To compare the subjects with and without COPD, Mann-Whitney U and Chi-square testing was used, where appropriate. Values of P_aCO_2, P_{ETCO2} and $P_{(a\text{-}et)}CO_2$ were tested for significance using Students T-test. For the comparison of P_aCO_2, P_{ETCO2} and $P_{(a\text{-}et)}CO_2$ between groups a two-tailed T-test was used. For comparison between P_aCO_2 and P_{ETCO2} a one-tailed T-test was used, since P_{ETCO2} will never exceed P_aCO_2. To compare Pearson's R for both groups we used the Fisher r-to-z transformation.

Additionally, Bland and Altman described in 2007 [19] that an adaptation was necessary in their method when multiple observations per subject were performed. To correct for these multiple measurements, weighted mean values were computed, and all CO_2 analyses mentioned above were also performed with these values.

Regarding the IPI™, mean IPI™ values with 95% confidence intervals were plotted against time. Also a comparison was made between subjects in which NIV was stopped because of clinical improvement and those who needed invasive mechanical ventilation or died. A regression coefficient was calculated, to assess a rise or fall in IPI™. Using the same statistics, a comparison was made between COPD and non-COPD subjects.

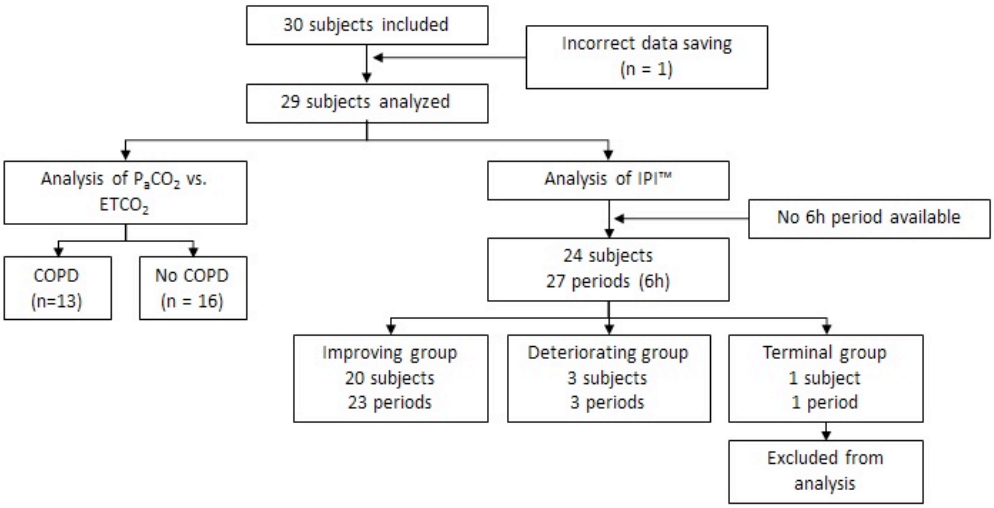

Figure 1: Flow-chart of included subjects and performed analyses.

3. RESULTS

3.1. Clinical Experience

Although we did not have any previous clinical experience with the Capnostream® monitor, setting up and operating the monitor was easy and quick. During measurements dislocation of the Microstream® Smart Capnoline® turned out to be a major problem. This was probably caused by restlessness, although the incidence of delirium, as diagnosed with CAM-ICU, was only 14% in the study population. Another explanation might be that the Microstream® Smart Capnoline® was obscured beneath the NIV facemask and so dislocation was not noticed immediately.

3.2. Study Population

In the study period (March – December 2012) thirty subjects were included after informed consent, see Figure **1**. Due to incorrect saving and hence loss of data, one subject could not be analyzed. The subject characteristics are described in Table **1**.

3.3. End-Tidal CO_2 Measurements

In the 29 analyzed subjects a total of 101 P_{ETCO2} measurements could be compared with corresponding P_aCO_2 values. There was a mean of 3 measurements per subject, ranging from 1 to 9 measurements. Mean P_aCO_2 was 41mmHg and mean P_{ETCO2} was 29mmHg. $P_{(a\text{-}et)}CO_2$ ranged from 1mmHg to 40mmHg with a mean difference of 13mmHg ($p < 0.001$). To assess correlation, Pearson's R was calculated: 0.65 ($p < 0.001$), see also Figure **2A**. Bland-Altman analysis [15] (Figure **2B**) shows that the majority of measurements is within the statistical limits of agreement.

Table 1: Subject Characteristics

Patient Characteristic	Median (Range)
Age	68(28–85)
APACHE II	16(6–33)
APACHE IV	63(15–136)
	Number (%)
Male/Female	20(69) / 9(31)
Start of NIV	
On admission	17(59)
During admission	8(27)
Direct post extubation	4(14)
Termination of NIV*	
Clinical improvement	20(69)
Intubation	6(21)
Death	1(3)
Reason of admission	
COPD	7(24)
Congestive heart failure	7(24)
Pneumonia	7(24)
Sepsis (other than respiratory)	4(14)
Pulmonary embolism	3(10)
Post surgery	1(3)
History	
COPD or asthma	13(45)
Heart disease	20(69)

*In two subjects NIV was not stopped on the ICU. One was discharged to the ward with NIV and one subject went to a specialized nursing home, while on NIV.

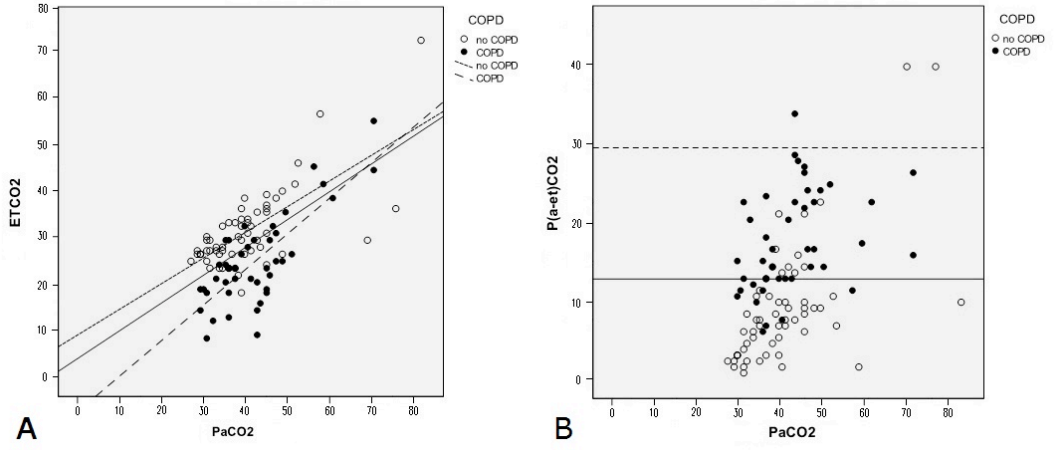

Figure 2A: P_{ETCO2} versus P_aCO_2 in mmHg. The undashed line indicates r for the total group. The dashed lines indicates subject groups with and without COPD. **B:** Modified Bland-Altman plot with $P_{(a\text{-}et)}CO_2$ versus P_aCO_2 in mmHg. The undashed line is the mean difference. The dashed line is de upper Limit of Agreement. The lower Limit of Agreement is below zero and not shown.

3.4. Comparison of Subjects with and without COPD

A comparison was made between COPD and non-COPD subjects. Baseline data are shown in Table **2**. No significant differences were found for age, sex or APACHE score. As to reason of admission, no significant difference was seen using Fisher-exact test.

Table 2: Comparison between COPD and Non-COPD Subjects

Parameter	Non-COPD	COPD	p-value
No.	16	13	-
Age	67.9	65.4	0.73
Male sex	11	9	0.56
APACHE II	19.1	17.5	0.50
APACHE IV	65.2	69.8	0.74

In COPD subjects 43 measurement were performed, in non-COPD subjects 58. Mean P_aCO_2 levels were 42 and 41mmHg respectively (p = 0.16), P_{ETCO2} levels were 25mmHg and 31mmHg ($p < 0.001$) and $P_{(a\text{-}et)}CO_2$ of 17 and 9mmHg respectively ($p < 0.001$). Correlation was plotted (see Figure **2A**) and Pearson's R was calculated for both groups resulting in r = 0.77 for measurements in COPD subjects and r = 0.70 in non-COPD subjects (both P < 0.001), see Figure **2A**. Difference between Pearson's R values of both groups was not statistically significant (p = 0.46).

A Bland-Altman plot was also made for COPD and non-COPD subjects (Figure **2B**). Majority of measurements was well between the statistical limits of agreement (LoA), with two extreme outliers in the non-COPD group. LoA were calculated for COPD (± 13mmHg) and non-COPD subjects (± 15mmHg) separately (not shown in Figure).

3.5. Correction for Multiple Measurements Per Subject

Mean values for P_aCO_2, P_{ETCO2} and $P_{(a\text{-}et)}CO_2$ did not differ compared to the method with individual observations. This also applied to mean data in the COPD and non-COPD groups. Pearson's R for the total group was 0.75 ($p < 0.001$), for subjects with COPD 0.86 ($p < 0.001$) and for subjects without COPD 0.89 ($p < 0.001$) (see Figure **3A**). Difference in Pearson's R between COPD and non-COPD was not significant (p = 0.27). Bland-Altman analysis is shown in Figure **3B**. Most notable is that all measurements in COPD subjects are above the mean $P_{(a\text{-}et)}CO_2$ of the total group.

3.6. Integrated Pulmonary Index™

IPI™ was analyzed every 15 minutes in the 6 hours before stopping NIV. An overview of eligible 6 hour periods for analysis is shown in Figure **1**. The subject which died was excluded from analysis because all treatment was discontinued, as this was considered futile. A complicating factor was that an IPI^{TM} value was missing in up to 42% of the time. This was most often

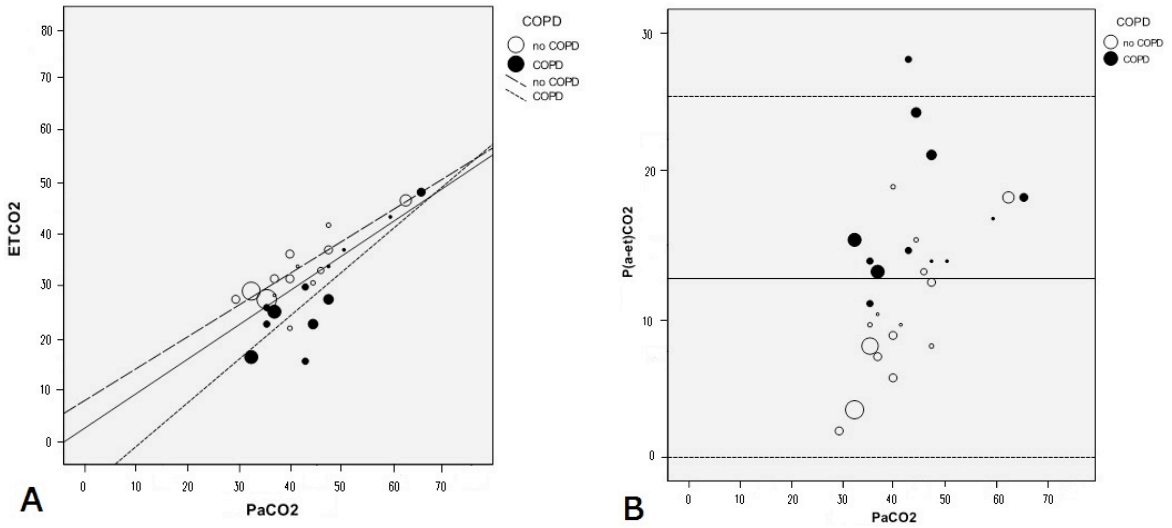

Figure 3A: P_{ETCO2} versus P_aCO_2 in mmHg after correction for multiple measurements per subject. Size of markers corresponds with number of measurements. The undashed line indicates r for the total group. The dashed lines indicate r for subject groups with and without COPD. **B:** Modified Bland-Altman plot with $P_{(a\text{-}et)}CO_2$ versus P_aCO_2 in mmHg after correction for multiple measurements per subject. Size of markers corresponds with number of measurements. The undashed line is the mean difference. The dashed lines are the Limits of Agreement.

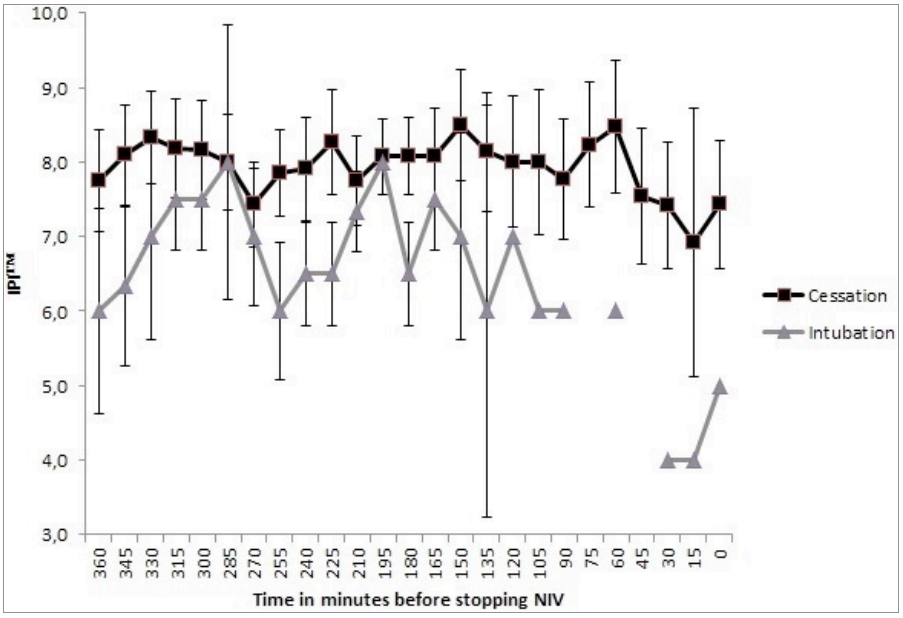

Figure 4: Integrated Pulmonary Index™ (IPI™) over time separately shown for subjects who were intubated and those who improved on NIV. Time on x-axis is displayed as minutes before intubation or stopping NIV. Where computable, a 95% confidence interval is shown.

due to no or incorrect measurement of one of the parameters required for IPI™ calculation. The IPI™ in the 6 hours before termination of NIV is shown in Figure **4**. Regression analysis revealed a non-significant negative correlation with r = 0.35 (p = 0.07) for improving subjects (group 1). For those deteriorating (group 2) no regression analysis could be performed, due to shortage of data. Remarkably IPI™ declined in both groups in the last hour before termination. Trend in IPI™ did not differ between COPD and non-COPD subjects, but IPI™ was slightly lower in COPD subjects, although not significant (mean 7.4 vs 7.9 respectively, p = 0.15).

3.7. Complications/Adverse Events of the Microstream® Smart Capnoline®

The study had to be terminated in one subject because the Microstream® Smart Capnoline® caused unacceptable amounts of leakage from the NIV-mask. In other subjects there were transient problems with mask leak, which in most cases was due to a concomitant nasogastric tube. No other adverse events or complications were encountered. In general, the Microstream® Smart Capnoline® was tolerated very well.

4. DISCUSSION

4.1. Results

Based on the results in individual measurements there was only a modest correlation between P_aCO_2 and P_{ETCO2}. When correction for multiple measurements per subject was performed, correlation improved for the total group and both subgroups (COPD and non-COPD) to an acceptable level. Hence, reliability of single measurements is only moderate, whereas a trend in P_{ETCO2} is more reliable.

Mean $P_{(a-et)}CO_2$ did differ significantly between both subgroups. Nevertheless, no significant difference between correlation coefficients was seen, so $P_{(a-et)}CO_2$ did not increase with rising P_aCO_2. The former can also be clearly seen in the Bland-Altman plots (Figure **2B** and **3B**), as the majority of the measurements in COPD are well above the line indicating the mean of measurements. Mean difference, as well as limits of agreement, did not meet the predetermined clinical cut-off values. Probably, this transgression of the cut-off values is mostly due to displacement of the Microstream® Smart Capnoline®, further mentioned below.

The analysis of the IPI™ was greatly hampered by an unacceptable high occurrence of missing data. Nonetheless, the available data showed that IPI™ was lower in the intubation group (Figure **4**) and in the COPD group (not significant), reflecting its property to objectify quality of respiration. Trend in IPI™ seemed to fall in deteriorating subjects, but was not significant. IPI™ did not significantly change over time in the improving population and in the non-COPD subgroup even a slight fall was seen, where an increase was to be expected. This fall was most prominent in the last hour before cessation of NIV. We have no exact

explanation for this decline in the improving subgroup, but an explanation could be that in the last hours before termination ventilator settings were minimalized and therefore respiratory parameters might have changed. Another explanation is that subjects might have been 'fighting the ventilator' causing distortion of measurements and eventually leading to cessation of NIV. This remains unclear.

4.2. Limitations

Obviously, this study has several limitations. Most prominent is the number of subjects included in this pilot study. The small number of subjects made it impossible to perform certain analyses, e.g. IPI™ analysis in subjects who required intubation. Also, COPD subjects were compared with non-COPD subjects. However, as mentioned in the introduction, there are numerous other conditions causing V/Q mismatching, e.g. pneumonia or pulmonary embolism. This study did not have the power to further analyze subjects susceptible for mismatching and to separately analyze them as a group. The presence of these conditions in both the COPD and non-COPD subgroup might have biased the results, although there was no difference in reason of admission.

Furthermore, patients with acute respiratory failure (ARF) and acute-on-chronic respiratory failure (ACRF) were analyzed together, although etiology and pathophysiology of the respiratory failure differs between groups. We attempted to correct for this condition by separating patients with COPD and without COPD in their medical history. Nevertheless, chronic respiratory failure and COPD are not the same entities. Formal subgroup analysis for ARF and ACRF could not be performed, because too little was known about the pre-admission pulmonary status of most patients. Despite the impossibility of such a formal post-hoc analysis, the lack in difference in reason of admission and baseline characteristics between COPD and non-COPD subjects, might indicate that COPD status can be seen as a derivative for the difference between ARF and ACRF.

Despite our efforts, not every blood gas measurement was exactly recorded on the Capnostream® monitor. In these cases we had to use the time of laboratory request. Although this time only varies a few minutes with the exact time of collection of the arterial blood gas sample, little variations in measurements might have occurred during this time.

The major problem we encountered during our study was displacement of the Microstream® Smart Capnoline®. When the Microstream® Smart Capnoline® was not in the right position (with the two nods in both nostrils), not all values, or lower values were measured, which of course impeded our measurements. Assessment of the Integrated Pulmonary Index™ (IPI™) was disappointing. Partially this was because of the frequent displacement, due to delirious or otherwise restless subjects. Also, IPI™ could only be calculated if all parameters were present, meaning that disturbance of measured side-stream P_{ETCO2}, respiration rate, heart rate or oxygen saturation would all lead to failure in calculating the IPI™.

Another cause of disappointing IPI™ results in this study might be, paradoxically, ICU treatment. In previous studies the IPI™ was used as an additive monitoring tool to detect deterioration in respiratory functioning. In case of such a decline in respiratory function, more experienced staff could be asked for help. In the ICU environment, respiratory function is monitored closely and staff is trained to optimize this function continuously. The measured parameters will therefore remain relative stable, due to these continuous interventions.

Summarizing, clinical value of side-stream P_{ETCO2} measurements was already established in different categories of non-ventilated subjects during procedures requiring sedation or in subjects in the PACU. Measurements during NIV were also available, but these studies comprised healthy volunteers on NIV and were primarily designed to identify the most reliable site of side-stream P_{ETCO2} measurement. Moreover, these groups, of course, lacked pathology requiring non-invasive ventilation. This was the first study of side-stream P_{ETCO2} in NIV, wherein real-life measurements were performed in subjects with pulmonary pathology, without any adjustments to normal clinical practice and also dealing with delirious or otherwise restless subjects.

5. CONCLUSION

This pilot study shows that side-stream P_{ETCO2} has a moderate to good correlation with P_aCO_2 in non-invasively ventilated non-COPD, as well as COPD subjects. There is, however, a lack of agreement between both values, exceeding clinical acceptable differences. Therefore, side-stream P_{ETCO2} measurements can be used to follow a trend in P_aCO_2, but exact values cannot replace P_aCO_2 measurements.

Analysis of IPI™ was greatly hampered by missing data. This was due to both Microstream® Smart Capnoline® displacement and the need for valid measurement of all parameters in order to calculate the IPI™. IPI™ could not identify and thereby predict which subjects would improve or deteriorate over time. Therefore, the clinical role of IPI™ as such parameter seems to be very limited in ICU subjects on NIV.

6. COMPLIANCE WITH ETHICAL STANDARDS

6.1. Funding

Oridion® Medical (currently Covidien) provided two Capnostream® monitors and enough tubing for this study and gave a research grant for study expenses. Study design was discussed with and approved by Oridion® Medical before the study commenced. Oridion® Medical was not involved in inclusion of subjects, data collection, data analysis nor in writing the manuscript. The study was conducted in the department of Intensive Care Medicine, in the Gelderse Vallei Hospital, Ede, The Netherlands.

6.2. Ethical Approval

This study was approved by the local ethics committee and all procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

6.3. Informed Consent

Informed consent was obtained from all individual participants included in the study.

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