Microstream end-tidal carbon dioxide and capillary carbon dioxide in mechanically ventilated extreme preterm neonates: a methods comparison study

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Research Article

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Abstract

Purpose: End-tidal carbon dioxide (ETCO2) is not routinely used in mechanically ventilated extreme preterm neonates due to the low tidal volume generated. Microstream devices potentially alleviate this problem as they need small sampl volumes. We compared micro stream ETCO2 and arterialized capillary PCO2 (PacCO2) in mechanically ventilated, extreme premature neonates for their correlation and agreement.

Methods: ETCO2 and PacCO2 were time matched. Repeated measures correlation coefficient was calculated, and Bland-Altman agreement plot was created. A linear mixed-effects model was developed.

Results: In the 49 pairs of ETCO2 and PacCO2, a moderately positive repeated measures correlation coefficient was observed [0.63 (0.4-0.81)]. A mean average monotonic bias of 22.6 mmHg was observed between PacCO2 and ETCO2. After controlling for mean airway pressure and respiratory rate, ETCO2 significantly predicted PacCO2 (b = 0.94 (0.39-1.5)).

Conclusions: Micro stream $ETCO_2$ and PacCO2 showed a moderately positive correlation but a high non-linear bias in mechanically ventilated, extreme preterm neonates in the first week of life. More research in larger and clinically diverse samples is required before routine clinical use

What Is Known?

- End-tidal CO2 measurement is a useful alternative to arterial PCO2 by providing continuous information about CO2 elimination in mechanically ventilated subjects
- Capillary PCO2 by heel puncture is a common method of CO2 assessment in neonatal intensive care units
- Reliability of ETCO2 is questionable in extreme preterm neonates due to the generation of small tidal volumes in these subjects

What is New?

- This study has compared microstream ETCO2 with capillary PCO2 (PacCO2) in mechanically ventilated extreme preterm neonates
- Micro stream $ETCO_2$ and PacCO2 showed a moderately positive correlation but a high non-linear bias between them
- More research in large and clinically diverse samples is required before using microstream ETCO2 in routine practice

Introduction

Adequacy of ventilation in mechanically ventilated neonates is assessed by the arterial or arterialized capillary partial pressure of carbon dioxide (PaCO2).[1] However, arterial PaCO2 is invasive, requires an indwelling arterial line, and is typically intermittent. Intermittent measurements are associated with a time lag between the actual change in CO2 in the internal milieu and the measured value of PaCO2, making the PaCO2 values less useful in real-time ventilation optimization. End-tidal carbon dioxide (ETCO2) measures the exhaled carbon dioxide (CO2) levels in the end-tidal gas with a sensor connected to either the mainstream or the side stream, the former more accurate than the latter.[2] TCO2 measurement has the advantage of being continuous, non-invasive, rapidly responsive to changes in the CO2 in the alveoli and can be represented both in numerical and graphical forms.[3]

Even though studies have shown the benefits of continuous CO2 monitoring in the acute care of ventilated neonates, neonatal intensive care units do not routinely use ETCO2 monitors for the monitoring of ventilation, primarily due to the limitations involved in the technology, the key among them being the volume of sample gas required to precisely measure the exhaled CO2 levels.[4] As extreme preterm neonates exhale low tidal volumes, the measurement of CO2 in such a small sample volume would require a highly sensitive device to reliably detect the CO2 levels in each ml of the gas sampled.[5] Microstream ETCO2 devices are essentially mainstream devices that typically require ~ 15 ml of sample gas volume for analysis.[6] Theoretically, even though microstream devices should solve the problem of low sample volume, published studies demonstrating the correlation and agreement of microstream ETCO2 with PaCO2 in mechanically ventilated preterm neonates are not available. Capillary blood samples are proxies for arterial samples for partial pressure of carbon dioxide (PCO2). Most studies have used arterial samples, whereas very few have used a mix of arterial and arterialized capillary (heel-prick) samples to measure PCO2 (PacCO2).[7] We report the results of a comparison of microstream ETCO2 and PacCO2 (arterial or arterialized capillary) in mechanically ventilated extreme preterm neonates in their first week of life.

Materials And Methods

This prospective 'methods comparison' study was conducted in a level III neonatal intensive care unit from September 2020 to June 2021. The study protocol was approved by the Institutional ethics committee. A written, informed consent was obtained from the parents. The study was performed in line with the principles of the Declaration of Helsinki. All preterm neonates < 30 weeks' gestation, < 7 days old, and required invasive mechanical ventilation in the NICU were included in the study. Those with cardiorespiratory malformations, circulatory instability, hypothermia in the preceding 12 hours, on high-frequency ventilation, and where parents refused consent were excluded.

ETCO2 was measured using the Microstream capnography ETCO2 module and capnoLine tube integrated into the Intellivue MX800 monitors (Microstream CO2 Extension, Philips India Limited, Gurgaon, Haryana, India). As per the manufacturer's recommendations, the ET module was calibrated each time before use to get a reliable respiratory cycle waveform and respiratory rates. The trend interval was set to the lowest possible averaging time. Arterial or arterialized CO2 (PacCO2) was measured in a

blood-gas analyzer (Radiometer India, Kurla, Mumbai, India). The analyzer uses a Clark electrode which measures the change in the current flowing through a reaction chamber where oxygen (O2) is reduced to OH^- ions by a change in voltage. All samples were processed within 30 minutes of sampling. Following pre-analytical precautions were taken: use of pre-heparinized syringes and capillaries, expelling the air bubbles by the standard recommended procedures, closing the syringe and capillary tips with caps, rotating the syringes and capillaries for uniform mixing of the heparin, entering the study subject's temperature and the fraction of inspired oxygen (FiO2) and repeated inversion of the syringe/capillary before inserting into the machine for processing.

As the study primarily assessed the correlation between one continuously monitored numerical variable (ETCO2) and another intermittently monitored numerical variable (PacCO2), the samples were time matched to ensure that they were representative of the physiological changes that took place in the internal milieu and were comparable on a time scale. For time matching, the actual time when the arterial/arterialized blood started to flow within the syringe or the capillary (depending on the method of blood sampling for arterial gas estimation) was noted down and documented to the accuracy of seconds. To facilitate reliable capturing of the actual time of the artery/capillary sampling, a second person (staff nursing officer) noted down the time. The values of ETCO2 corresponding to the arterial sampling time were noted down for analysis to the accuracy of ± 30 seconds. While the samples were drawn for ABG analysis, the ETCO2 values were documented.

Blood gas analyses were performed at the treating clinician's discretion, which depended primarily on the underlying lung disease, acute or convalescing lung disease, and settings on the ventilator. All the collected samples were analysed, and each pair of measurements of ETCO2 and PacCO2 were available for analysis (no missing data, equivalent to the intention to treat analysis in an intervention trial). PacCO2 was analysed independent of ETCO2. This meant that the PacCO2 assessor (principal investigator) was not aware of the ETCO2 value till the blood sample was processed in the blood gas analyser.

Sample size and statistical analysis

As the correlation coefficient (r) between PacCO2 and microstream ETCO2 (primary outcome variable) was not known, we assumed no correlation exists between them (null hypothesis). To reject the null hypothesis and for an expected correlation coefficient of 0.5 (assumed) with a two-sided alpha error of 0.05 and beta error of 0.1, we required 38 samples*. To account for missing data at random of ~ 20%, a total sample size of 46 was required.

*$N=[(Za + Zb)/C]2 + 3$; (Za is 1.96 for an alpha error of 0.05; Zb is 1.282 for a beta error of 0.10; $C = 0.5X\ln[(1 + r)/(1-r)]$)

N is the total number of subjects required, and 'r' is the expected correlation coefficient (assumed as 0.5 in the current calculation).

Data were analyzed using the R language for statistical computing and specific packages.[8] Descriptive measures such as mean, median, range, and standard deviation (SD) were calculated for continuous data. Normality assumption was tested with an appropriate test. Due to more than one pair of measurements from each subject (repeated measures), inter- and intra-rater reliability could not be assessed by calculating the intra-class correlation coefficient (ICC) as it will be erroneous. Hence, a correlation between ETCO2 and PacCO2 was examined by repeated-measures correlation coefficient (RM - Correlation). Locally weighted smoothing regression (LOESS) method was used for scatter plot regression lines. Bland-Altman plots for agreement were created, and mean difference (agreement) and their 95% confidence intervals were calculated. As the data had multiple levels (hierarchical data) as well as repeated measures with unequal time points of measurements, a mixed linear model was used for regression. A two-tailed p-value of < 0.05 was considered as significant.

Results

Out of the 141 neonates who required mechanical ventilation during the study period, 63 received ventilation in the first week of life. Of them, 50 were excluded (refusal of consent – 9, cardiorespiratory abnormalities – 25, hypotensive shock – 16). The remaining 13 preterm neonates contributed to 49 pairs of PacCO2 and ETCO2 during the study period. The mean gestation and birth weight of the study population were 26.5 ± 2 weeks and 935 ± 270 grams, respectively (Table 1). The Median (IQR) age at initiation of mechanical ventilation in the study population was 104 (76–144) hours. Median (IQR) ETCO2 and PacCO2 of all the 49 pairs of measurements were 27 (22–33) mmHg and 50 (43–60) mmHg, respectively (Fig. 1).

Table 1
Demographic and clinical characteristics of the study population (n = 13)

S. No	Characteristic	Value Mean ± SD; Median (IQR)
1	Gestation (weeks)	26.5 ± 2
2	Birth weight (grams)	935 ± 270
3	Male gender; n (%)	10 (78)
4	Small for gestational age; n (%)	3 (23)
5	Pregnancy induced hypertension; n (%)	6 (46)
6	Gestational diabetes Mellitus; n (%)	2 (15)
7	Preterm premature rupture of membranes; n (%)	6 (46)
8	Maternal antenatal corticosteroids; n (%)	5 (39)
9	Apgar score at 5 minutes	6 (5–7)
10	Apgar score at 10 minutes	8 (8–8)
11	Required resuscitation; n (%)	6 (46)
12	Age at initiation of mechanical ventilation (h)	104 (76–144)
13	Indication for mechanical ventilation; n (%) # • Respiratory distress syndrome • Apnea	12 (92) 3 (8)
14	Required CPAP before intubation; n (%)	13 (100)
15	Required NIPPV before intubation; n (%)	3 (23)
16	Received surfactant before intubation; n (%)	8 (62)
17	Duration of non-invasive ventilation before intubation (h)	43 ± 19; 40 (33–52)
18	Mean airway pressure (cm H2O)*	7.6 ± 1.1
19	Tidal volume (ml/kg)*	6.5 ± 1.8
20	Respiratory rate (ventilator) (bpm)*	42 ± 4

Abbreviations: bpm – breaths per minute, CPAP – continuous positive airway pressure, NIPPV – non-invasive positive pressure ventilation, PaCO2 – partial pressure of carbon dioxide, ETCO2 – end-tidal carbon dioxide

Numbers do not add up to total as categories are not mutually exclusive

* Measurements made at the same time point as that of CO2 measurement

S. No	Characteristic	Value Mean ± SD; Median (IQR)
21	Respiratory rate (spontaneous + ventilator) (bpm)*	60 ± 11
22	PaCO2 (mmHg)	51.7 ± 13
23	ETCO2 (mmHg)	29.2 ± 10.1
Abbreviations: bpm – breaths per minute, CPAP – continuous positive airway pressure, NIPPV – non-invasive positive pressure ventilation, PaCO2 – partial pressure of carbon dioxide, ETCO2 – end-tidal carbon dioxide		
# Numbers do not add up to total as categories are not mutually exclusive		
* Measurements made at the same time point as that of CO2 measurement		

The repeated measures correlation coefficient (RM – correlation) between ETCO2 and PacCO2 was 0.65 (95% C.I: 0.40–0.81, p < 0.001) (Fig. 2). The mean average bias (average of differences) between PacCO2 – ETCO2 (95% C.I) in the Bland-Altman method of agreement testing was 22.6 (18.5–26.7), indicating a monotonic overall bias towards a higher PacCO2 value for each ETCO2 value (Fig. 3). The plot also reveals a drift towards higher values in the difference as the mean values increased, indicating an associative relationship between PacCO2 and ETCO2. This was further emphasized by observing a positive correlation between the differences in ETCO2 and PacCO2 and their average (Spearman's rho: 0.35 (0.07–0.57), p = 0.01).

To further explore the relationship, a linear mixed-effects model was fit by the maximum likelihood method with PacCO2 as a dependent variable, ETCO2 as the independent variable (fixed effect), and ETCO2 was allowed to randomly vary between subjects (random effects). The model also included mean airway pressure (MAP) and respiratory rates (RR) as fixed effect covariates. The model was derived in a stepwise fashion first by allowing the intercept (PacCO2) to randomly vary between subjects (termed as random intercepts) and then by allowing the ETCO2 to randomly vary between subjects (termed as random slopes). We observed that the relationship between PacCO2 and ETCO2 showed significant variance in intercepts across subjects, SD = 16.05 (95% C.I: 7.3, 35.2), c2 (1) = 8.38, p = 0.004, meaning that each subject had a different intercept. In addition, the slopes also significantly varied across subjects, SD = 0.69 (95% C.I: 0.37, 1.3), c2 (2) = 14.13, p < 0.001 and the slopes and intercepts were negatively and significantly correlated, -0.93 (-0.99, -0.55). ETCO2 significantly predicted PacCO2, b = 0.94 (95% C.I: 0.39, 1.5), t (35) = 3.29, p = 0.002, after controlling for mean airway pressure (MAP) measured in the ventilator and the total respiratory rate (RR). The regression equation of the mixed-effects model is: PacCO2 (mmHg) = 26.9 (13–41) + 0.94 (0.4–1.5) * ETCO2 in mmHg.

Discussion

Continuous, non-invasive monitoring of ETCO2 offers a useful alternative to PacCO2 for ventilation adequacy assessment. This assumes a greater role in preterm neonates who are at a higher risk of sepsis

and anemia due to invasive blood sampling. Studies comparing a microstream capnography device with PCO2 measured from a capillary blood sample (PacCO2) are scarce in the literature. With this rationale, we compared PacCO2 with ETCO2 in mechanically ventilated preterm neonates of < 30 weeks' gestation in their first week of life. The key observations were: a) ETCO2 showed a moderate positive repeated measures correlation coefficient of 0.63 with PacCO2, b) barring three pairs of observations, the remaining 46 pairs of observations of ETCO2 and PacCO2 were observed to lie within the limits of agreement (LoA) in a Bland-Altman plot indicating a good agreement between these two measures, c) the relationship between ETCO2 and PacCO2 was monotonous (uni-directional) but non-linear in nature as shown by the relatively lower PacCO2 as the ETCO2 approached towards higher values and d) a linear mixed-effects model showed that ETCO2 significantly predicted PacCO2 controlling for the effects of mean airway pressure and respiratory rate.

The current study was different from the previous studies in a few important aspects. We included only mechanically ventilated, extreme preterm neonates, a subset where ETCO2 would be more useful. As this subset would inherently generate a low tidal volume of 1 to 3 ml/kg, we used a microstream device instead of the conventional mainstream and sidestream devices. Microstream devices (15 microlitre sample cell) can accept sample gas volume as low as 0.05 L/min flow for analysis of CO2 and hence would potentially be more useful in premature neonates who typically generate small tidal volumes. A recent scoping review of 18 studies on methods of assessment of CO2 reported that all the studies reported strong correlation and agreement between the methods with moderate correlation in gestation < 37 weeks.[7] However, none have reported having used a microstream device to measure ETCO2. We included only those neonates who were mechanically ventilated in their first week of life to compare the two methods while the cardio-pulmonary transition is still taking place.

As the study subjects contributed to the observations (samples) more than once (repeated measurements), instead of a simple correlation assessment, which would have been an erroneous method in such designs, we used a repeated measures correlation approach by including the between-subjects variability in the model. Moreover, a mixed model (multi-level) regression was done for the prediction of PacCO2 from ETCO2 due to the hierarchical nature of the study. We observed that for every 10 mmHg increase in ETCO2, the PacCO2 would increase by 9.2 mmHg over and above 26.9 mmHg (PacCO2 value when ETCO2 is zero). This relation further emphasizes the non-linear association between PacCO2 and ETCO2, meaning that for every 10 mmHg movement of ETCO2 towards the higher side, there will be a shortfall of 0.8 mmHg movement in PacCO2 in the same direction.

Respiratory distress syndrome and pneumonia were the two most common illnesses observed in the current study. ETCO2 measurements are expected to be lower than PaCO2 due to increased dead space ventilation and intra-pulmonary shunting as it occurs in severe parenchymal lung disease, impediment in the alveolar phase of ETCO2 measurement in infants with high respiratory rates, and inaccurate measurements due to peri tubal leak in uncuffed endotracheal tubes.[9] Bhat and Abhishek as well as Hagerty et al., showed a higher gradient between PaCO2 and ETCO2 in infants ventilated for pulmonary disease compared to those ventilated for non-pulmonary conditions.[10, 11] Nangia et al. reported a

relatively lower correlation coefficient of 0.55 in the respiratory distress syndrome group of preterm neonates.[12] Williams et al. reported that V/Q mismatch in severe lung disease is associated with erratic ETCO2 values and poor correlation between ETCO2 and PaCO2.[13] However, Nakato et al. reported a comparable correlation in neonates both with and without diffuse parenchymal lung disease.[14] It is noteworthy that all the above studies compared PaCO2 with ETCO2. We observed a high bias between PacCO2 and ETCO2. The presence of an underlying lung disease causing a higher PacCO2 and a lower ETCO2, thereby widening the gradient and predominant use of capillary blood for PacCO2 measurements, could be the two important reasons for the high bias observed.

One major limitation of the current study is the inability to stratify and compare the effect of several types of pulmonary pathologies on the correlation between ETCO2 and PacCO2, due primarily to the limited sample size. Nevertheless, we used mean airway pressure as a disease-agnostic respiratory severity measure in the regression model. We also did not use a control group (without co-existing lung disease) to show that co-existing lung pathology would confound the relation between these two methods of CO2 assessment due to the non-availability of enough subjects who were primarily ventilated for a non-respiratory problem.

To conclude, in this first study which has compared microstream ETCO2 with arterialized capillary PCO2 in the extreme preterm population, we have observed a moderate repeated measures correlation of 0.63 between these parameters. A linear mixed-effects model has shown that ETCO2 can predict PacCO2 significantly after controlling for mean airway pressure and respiratory rates. A high bias exists between microstream ETCO2 and PacCO2, thus warranting larger studies comparing these two methods stratified for various pulmonary morbidities to better understand their relationship.

Statements And Declarations

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Competing interests: The authors have no relevant financial or non-financial interests to disclose

Availability of data and material: Data and material will be available from the corresponding author on reasonable request for the purpose of a systematic review

Code availability: All the codes related data analysis will be available from the corresponding author on a reasonable request

Ethics approval: The study was performed in line with the principles of the Declaration of Helsinki and the study protocol had obtained approval from the Institute Ethics Committee prior to enrolling the first subject

Consent to participate: Informed and written consent was obtained from one of the parents of each individual participants of the study

Consent to publish: Not applicable

Author contributions:

Boyapally VK contributed to the study design, data acquisition and drafting of the manuscript. He made the final approval of the version

Sundaram VS conceptualized and designed the study, analyzed the data, revised the manuscript, and gave the final approval of the version

Kumar P and Kumar J contributed to the study design and analysis and interpretation of the data, critically revised the content, and gave the final approval of the version to be published

All the authors did agree to be accountable for all aspects of the work related to accuracy or integrity of the work

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Figures

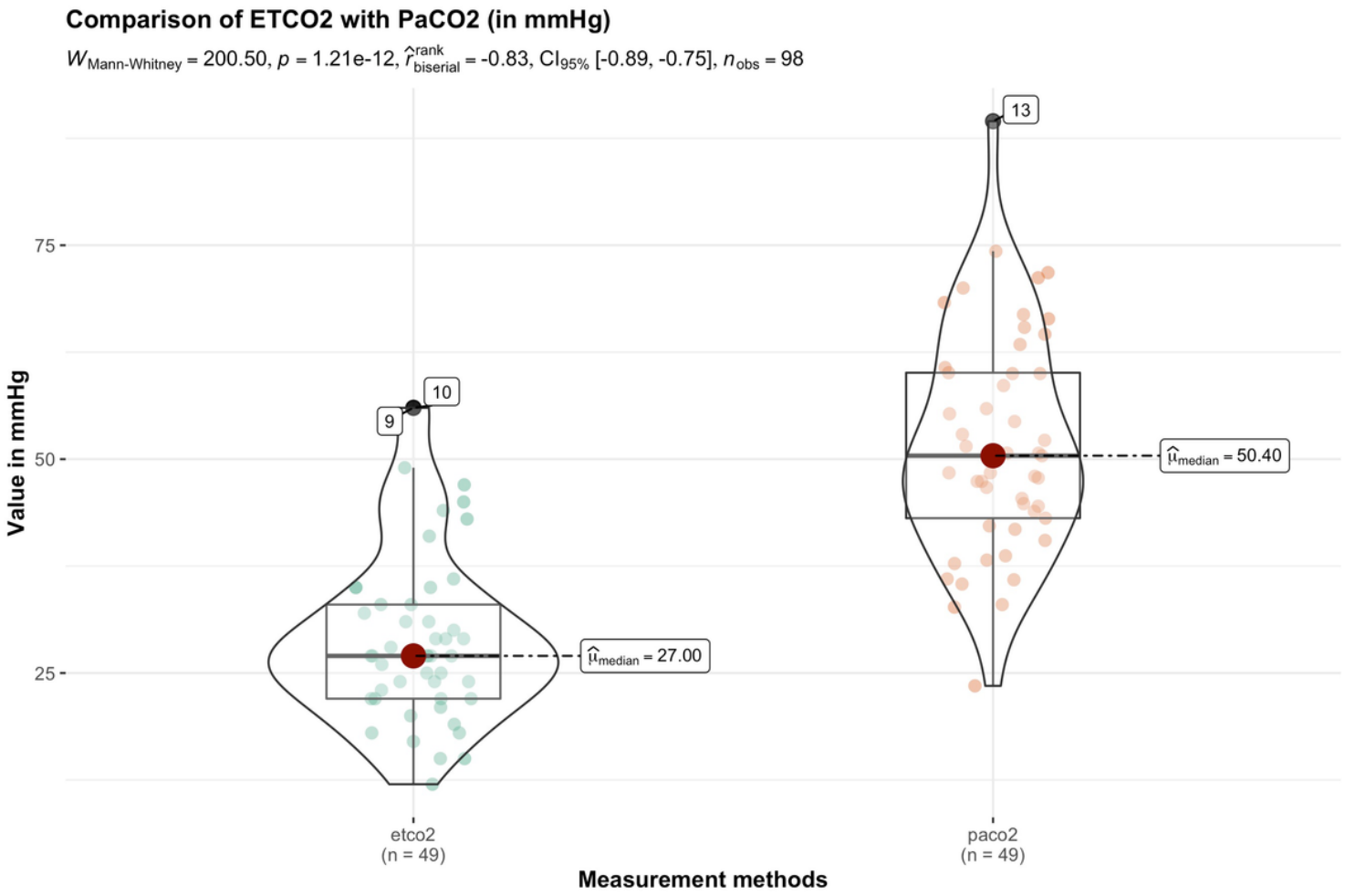

Figure 1

Box & Violin plot comparing PacCO2 with ETCO2

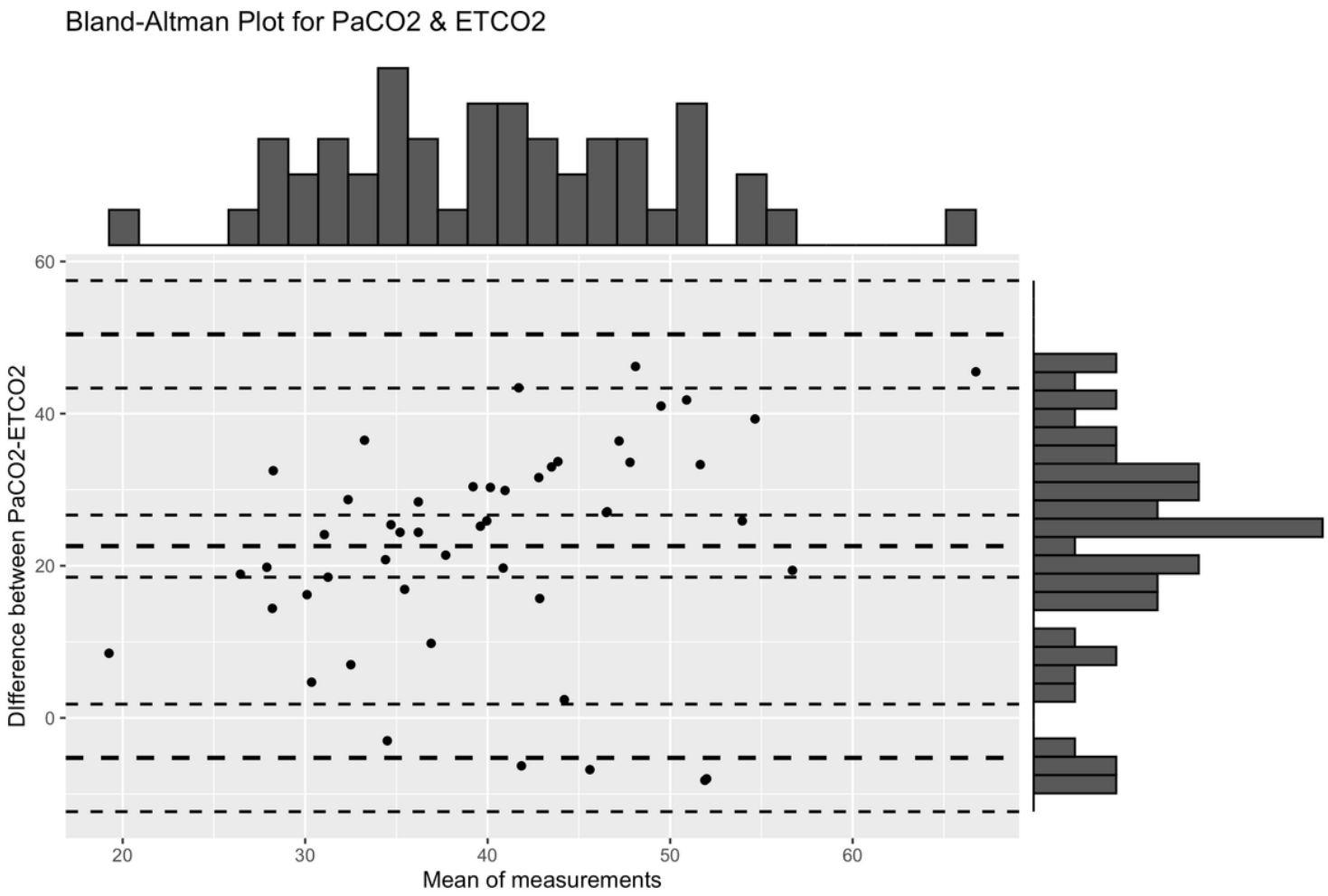

Figure 2

Bland-Altman agreement plot with marginal histogram

Note: Bland-Altman agreement plot with superadded marginal (average) plot demonstrating the distribution of average and differences of $PacCO_2$ and ETCO2

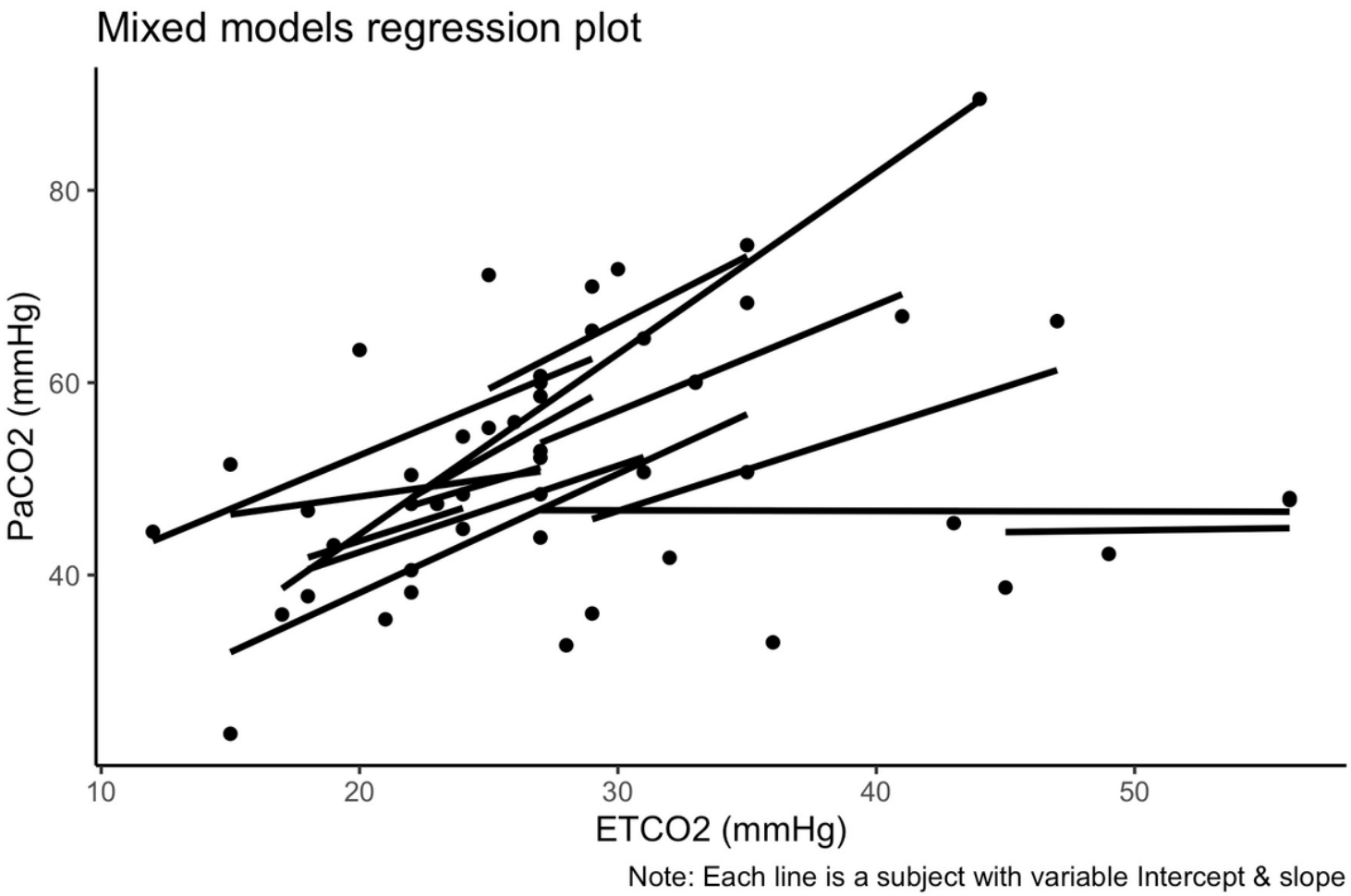

Figure 3

Repeated measures correlation plot

Supplementary Files

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