Comparison of mainstream end tidal carbon dioxide on Y-piece side versus patient side of heat and moisture exchanger filters in critically ill adult patients: a prospective observational study

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Abstract
The purpose of the study was to investigate the accuracy of mainstream EtCO2 measurements on the Y-piece (filtered) side of the heat and moisture exchanger filter (HMEF) in adult critically ill patients, compared to that on the patient (unfiltered) side of HMEF. We conducted a prospective observational method comparison study between July 2019 and December 2019. Critically ill adult patients receiving mechanical ventilation with HMEF were included. We performed a noninferiority comparison of the accuracy of EtCO2 measurements on the two sides of HMEF. The accuracy was measured by the absolute difference between PaCO2 and EtCO2. We set the non-inferiority margin at +1 mmHg in accuracy difference between the two sides of HMEF. We also assessed the agreement between PaCO2 and EtCO2 using Bland–Altman analysis. Among thirty-seven patients, the accuracy difference was −0.14 mmHg (two-sided 90% CI −0.58 to 0.29), and the upper limit of the CI did not exceed the predefined margin of +1 mmHg, establishing non-inferiority of EtCO2 on the Y-piece side of HMEF (P for non-inferiority < 0.001). In the Bland–Altman analyses, 95% limits of agreement between PaCO2 and EtCO2 were similar on both sides of HMEF (Y-piece side, −8.67 to +10.65 mmHg; patient side, −8.93 to +10.67 mmHg). The accuracy of mainstream EtCO2 measurements on the Y-piece side of HMEF was noninferior to that on the patient side in critically ill adults. Mechanically ventilated adult patients could be accurately monitored with mainstream EtCO2 on the Y-piece side of the HMEF unless their tidal volume was extremely low.

Keywords Capnography · End-tidal carbon dioxide · Humidifier · Intensive care unit · Mechanical ventilation · Monitoring

Abbreviations
CI Confidence interval
CO2 Carbon dioxide
EtCO2 End-tidal carbon dioxide
HMEF Heat and moisture exchanger filter
ICU Intensive care unit
IQR Interquartile range
PaCO2 Partial pressure of arterial carbon dioxide
PEEP Positive end expiratory pressure
SD Standard deviation

1 Introduction
End-tidal carbon dioxide (EtCO2) monitoring is a non-invasive, continuous measurement of exhaled carbon dioxide (CO2) that offers real-time information about patients’ ventilation, perfusion, and metabolism [1–4]. In ICU, EtCO2 monitoring ensures the integrity of the ventilator circuit and assists the titration of mechanical ventilation...
[5]. Furthermore, a detailed assessment of EtCO2 provides valuable insights into pathological respiratory physiology, such as increased physiologic dead space in critically ill patients [5]. The importance of EtCO2 monitoring for patient safety has been increasingly recognized, and many professional societies have adopted its use as a standard of practice [3].

Heat and moisture exchanger filters (HMEFs) are widely used humidifier devices, especially during the current coronavirus disease 2019 pandemic for their filtering function. In ventilator circuits with HMEF, an EtCO2 sensor is placed either on the patient side or the Y-piece side of HMEF. On the patient side, exhaled gas reaches an EtCO2 sensor before being filtered by HMEF, thereby coughed up secretions from patients can contaminate the sensor and interrupt continuous monitoring. On the Y-piece side, in contrast, the exhaled gas is measured after being filtered by the HMEF, reducing the risk of sensor contamination. Current anesthesia guidance during the coronavirus disease 2019 pandemic recommends using an HMEF and sampling gas from the Y-piece (filtered) side of HMEF. On the patient side, exhaled gas reaches an EtCO2 sensor before being filtered by HMEF, thereby coughed up secretions from patients can contaminate the sensor and interrupt continuous monitoring. On the Y-piece side, in contrast, the exhaled gas is measured after being filtered by the HMEF, reducing the risk of sensor contamination. Current anesthesia guidance during the coronavirus disease 2019 pandemic recommends using an HMEF and sampling gas from the Y-piece (filtered) side of HMEF [6]. However, HMEF alters the components of exhaled gas during filtering, and thus affects EtCO2 values and waveforms [7]. Previous studies reported that EtCO2 measured with the sidestream method on the Y-piece side of HMEF showed lower values than that on the patient side [8, 9]. Inaccurately low EtCO2 values could lead to misrecognition of CO2 retention and threaten patient safety [10].

In the ICU, the mainstream EtCO2 measurement is preferred because it has a faster response time than the sidestream method [5]. Yet, the accuracy of mainstream EtCO2 on the Y-piece side of HMEF has not been evaluated [5]. This study aimed to investigate whether the accuracy of mainstream EtCO2 measurement on the Y-piece side of the HMEF was noninferior to that on the patient side in critically ill adult patients receiving mechanical ventilation. This non-inferiority design is based on the benefits conferred by HMEF when measuring on the Y-piece side.

2 Methods

2.1 Study design and setting

This study was approved by the institutional review board (2019-No.17). The requirement for written informed consent was waived by the institutional review board. The protocol was registered a priori in the UMIN-CTR (UMIN-CTR ID: 000037317).

This was a single-center prospective observational method comparison study in a tertiary care teaching hospital in Japan, which had 550 beds with 12 general ICU beds, conducted between July 2019 and December 2019.

2.2 Selection of the patients

We prospectively screened all patients of mechanical ventilation in the ICU between July 16, 2019, and December 9, 2019. Patients were eligible when they were adults (≥ 20 years) receiving invasive mechanical ventilation, HMEF was used in the ventilator circuit, and an arterial line was placed. Patients were excluded when they were pregnant, previously enrolled in this study, patients or next of kin refused study participation, or they met any of the following safety criteria. The safety criteria were: PEEP ≥ 10 cmH2O, fraction of inspired oxygen ≥ 0.6, heart rate < 40 bpm or 130 ≥ bpm, mean blood pressure < 60 mmHg or ≥ 110 mmHg, saturation of percutaneous oxygen < 90%, respiratory rate ≥ 40 breaths/min, or temperature < 36 or ≥ 38.5 °C. These criteria followed the Japanese guidelines for early mobilization of mechanically ventilated patients [11, 12]. We also excluded patients when treating physicians judged the patient as inappropriate for study participation.

2.3 Measurement of EtCO2

For eligible patients, we measured EtCO2 on the two sides of the HMEF and PaCO2 during the daytime (8:00–17:00) on weekdays. The timing of the measurements was based on the clinical indication of arterial blood gas analysis. We measured the first EtCO2 on either the Y-piece side or the patient side of the HMEF, where the EtCO2 sensor was placed (Fig. 1). Then, we switched the EtCO2 sensor to the opposite side of the HMEF and measured the second EtCO2. On each side, we averaged EtCO2 from three consecutive breaths to prevent errors caused by drift during recording and to obtain values that sufficiently represent respiratory status at the time of measurement [8, 9]. CO2 sensor zeroing was performed when we switched the position of the sensor, or the baseline flow did not return to zero in the capnography. Clinical engineers in the study team measured EtCO2, simultaneously collected arterial blood, and submitted it for blood gas analysis to measure PaCO2. Each EtCO2 reading was performed before the results of blood gas analysis returned; thus, readers of EtCO2 were unaware of the PaCO2 value. The EtCO2 sensor was Capnostat5 (Respironics), HMEF was Hygrobag S (Medtronic), and the blood gas analyzer was ABL800 (RADIOMETER).

We recorded patient demographics and clinical characteristics, including acute physiology and chronic health evaluation II (APACHE II) scores evaluated with the worst
values during the first 24-h in the ICU [13], vital signs, and ventilatory parameters evaluated at the time of EtCO2 measurement, as shown in Tables 1 and 2. All patients were followed up until hospital discharge, and hospital outcomes were recorded.

2.4 Statistical analysis

We labeled EtCO2 measured on the Y-piece side of HMEF as “the index measurement,” EtCO2 measured on the patient side as “the alternative measurement,” and PaCO2 as “the reference standard [14].” We assessed the accuracy of EtCO2 measurements by the absolute difference between PaCO2 and EtCO2 [15]. We defined ΔY-piece side as the absolute difference between PaCO2 and EtCO2 measured on the Y-piece side of HMEF, and Δpatient side as the absolute difference between PaCO2 and EtCO2 measured on the patient side. We compared the accuracy of the two EtCO2 measurements by the accuracy difference defined as ΔY-piece side—Δpatient side. We calculated the accuracy difference in each patient and estimated the mean and two-sided 90% CI.

In the non-inferiority comparison of accuracies of the two EtCO2 measurements, we set a priori the non-inferiority margin of +1 mmHg in accuracy difference. The size of the margin was determined from a clinical standpoint and previous reports [8, 9, 16]. We declared non-inferiority of the Y-piece side if the upper limit of the CI for accuracy difference did not exceed the predefined margin of +1 mmHg. This means that we accepted the Y-piece side if the absolute difference between PaCO2 and EtCO2 on the Y-piece side was not more than +1 mmHg compared to the absolute difference between PaCO2 and EtCO2 on the patient side. We calculated the P-value for non-inferiority using two one-sided paired-sample t-tests. From the pilot observation, SD of the accuracy difference between the Y-piece side and the patient side was estimated at 1.5 mmHg. The calculated sample size for the non-inferiority test was 35 paired observations with a 5% one-sided significance level and 90% power [17, 18].

In addition, on each side of the HMEF, we assessed the agreement between PaCO2 and EtCO2 using Bland–Altman analysis [19]. We graphically presented the variation of differences between PaCO2 and EtCO2 against their average (Bland–Altman plot). As a measure of lack of agreement, we estimated the mean difference and 95% limits of agreement [19]. We performed Bland–Altman analysis for EtCO2 on the Y-piece side and EtCO2 on the patient side separately, then compared the graphics and statistics of the two analyses. According to the reporting standards for Bland–Altman analysis, to ensure that the limits of agreement were meaningful summary statistics of the differences, we checked the following assumptions: repeatability, normality, and constant variation. Repeatability represents within-patient variation in repeated measurements of EtCO2 in the same patient [20]. We recorded three EtCO2 measurements per position per patient and assessed the repeatability of EtCO2. We graphically checked whether the differences were normally distributed and whether variations in the differences were constant across the range of measurements. We also performed Shapiro–Wilk test for normality.

Previous studies reported that differences between EtCO2 on the Y-piece side and EtCO2 on the patient side of HMEF were greater when the tidal volume was small [8, 9]. Therefore, we evaluated the relationship between the differences and tidal volume using Pearson’s correlation coefficient and linear regression.

We presented patient characteristics as medians with interquartile ranges (IQR) for continuous variables and as proportions for categorical variables. We presented paired observations of EtCO2 values, absolute differences, and ventilator monitoring values on the two sides of the HMEF as means with SDs. The means of differences between paired observations were compared with paired samples t-test, and two-sided P-values were reported. All statistical analyses were performed using R (The R Foundation for Statistical Computing, ver.3.5.2) and EZR (Saitama Medical Center, Jichi Medical University, ver.1.40), which is a graphical
Figures 3, 4 and Supplemental Fig. 1 (Supplementary Information 1) were created using JMP (ver.16.1.0).

### 3 Results

Between July 16, 2019, and December 9, 2019, there were 167 patients on mechanical ventilation in the ICU, and screening for full eligibility criteria was completed in 132 of them (Fig. 2). Among the 52 eligible patients, we excluded 15 that met the exclusion criteria, leaving 37 patients in the study. In all 37 patients, two EtCO2 measurements and PaCO2 were collected. The median age was 70 years (IQR, 60–79), 57% (21/37) were male, 76% (28/37) were emergency ICU admissions, and the median acute physiology and chronic health evaluation II score was 19 (IQR, 16–25) (Table 1). The major diagnoses were cardiovascular [19% (7/37)], respiratory [11% (4/37)], gastrointestinal [27% (10/37)], and neurological diseases [22% (8/37)].

At the time of EtCO2 measurements, the median number of days from ICU admission was 2 days (IQR, 2–2), and the median time from intubation was 21 h (IQR, 14–24). Most of the patients had stable vital signs; the median systolic blood pressure was 129 mmHg (IQR, 109–144), body temperature was 36.9 °C (IQR, 36.6–37.4), and respiratory rate was 16 breaths per minute (IQR, 14–19). The median partial pressure of arterial oxygen was 93.0 mmHg (IQR, 83.8–124.0), PaCO2 was 38.2 mmHg (IQR, 34.9–41.6), and the ratio of partial pressure arterial oxygen to fraction of inspired oxygen was 364 (IQR, 317–410). The ventilator mode was continuous spontaneous ventilation in 46% (17/37) of the patients. The median fraction of inspired oxygen was 0.25 (IQR, 0.21–0.35) and PEEP was 5 cmH2O (IQR, 5–5). The median ICU stay was 4 days (IQR, 2–7), and the hospital mortality rate was 16% (6/37).

The paired observations on the Y-piece side and the patient side of the HMEF are presented in Table 2. The means of EtCO2 were 37.4 mmHg (SD, 5.5) and 37.5 mmHg (SD, 6.1) on the Y-piece side and the patient side, respectively. The mean difference in EtCO2 (Y-piece side—patient side) was -0.1 (SD, 1.6). The estimated accuracy difference (ΔY-piece side—Δpatient side) was −0.14 mmHg (two-sided 90% CI −0.58 to 0.29). The upper limit of the CI for accuracy difference did not exceed the predefined margin of +1 mmHg, establishing non-inferiority (P for non-inferiority < 0.001) (Fig. 3).

In the Bland–Altman analyses, the mean difference between PaCO2 and EtCO2 on the Y-piece side was 0.99 mmHg (95% CI –0.66 to 2.63), and 95% limits of agreement was −8.67 mmHg (95% CI –11.51 to –5.84) to 10.65 mmHg (95% CI 7.82–13.49). The mean difference between PaCO2 and EtCO2 on the patient side was

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**Table 1 Patients Demographics, Characteristics at EtCO2 measurements and Outcomes**

| Variables | N = 37 |
|-----------|--------|
| **Demographics** | |
| Age (median [IQR]) | 70 [60–79] |
| Male (%) | 21 (57%) |
| BMI (median [IQR]) | 21.8 [19.6–25.3] |
| Current or former smoker (%) | 17 (46%) |
| Location prior to ICU admission (%) | |
| Operating room | 20 (54%) |
| Emergency room | 11 (30%) |
| Ward | 6 (16%) |
| **ICU admission diagnosis (%)** | |
| Cardiovascular | 7 (19%) |
| Respiratory | 4 (11%) |
| Gastrointestinal | 10 (27%) |
| Neurological | 8 (22%) |
| Metabolic | 2 (5%) |
| Genitourinary | 1 (3%) |
| Obstetrics and gynecology | 2 (5%) |
| Musculoskeletal | 1 (3%) |
| Trauma | 2 (5%) |
| **APACHE II score (median [IQR])** | 19 [16–25] |
| **Characteristics at EtCO2 measurements** | |
| Time from intubation (median [IQR]), hour | 21 [14–24] |
| Days from ICU admission (median [IQR]), day | 2 [2–2] |
| **Vital signs during measurement (median [IQR])** | |
| Systolic blood pressure, mm Hg | 129 [109–144] |
| Diastolic blood pressure, mm Hg | 63 [56–72] |
| Mean arterial pressure, mm Hg | 88 [77–101] |
| Heart rate, /min | 82 [72–95] |
| Body temperature, Celsius | 36.9 [36.6–37.4] |
| Percutaneous oxygen saturation (%) | 98 [97–99] |
| **Arterial blood gas analysis and ventilator settings (median [IQR])** | |
| PaCO2, mm Hg | 38.2 [34.9–41.6] |
| PaO2, mm Hg | 93.0 [83.8–124.0] |
| pH | 7.43 [7.42–7.45] |
| Bicarbonate, mmol/L | 25.3 [22.5–27.1] |
| P/F ratio | 364 [317–410] |
| FiO2 | 0.25 [0.21–0.35] |
| PEEP, cm H2O | 5 [5–5] |
| **Patient outcomes** | |
| ICU stay (median [IQR]), day | 4 [2–7] |
| Survival discharge | 20 (54%) |
| Transfer | 11 (30%) |
| Death | 6 (16%) |

*EtCO2* end-tidal carbon dioxide, *IQR* interquartile range, *BMI* body mass index, *ICU* Intensive Care Unit, *APACHE* acute physiology and chronic health evaluation, *PaCO2* partial pressure of arterial carbon dioxide, *PaO2* partial pressure of arterial oxygen, *P/F* ratio the ratio of arterial oxygen partial pressure to fraction of inspired oxygen, *FiO2* fraction of inspired oxygen, *PEEP* positive end expiratory pressure.
0.87 mmHg (95% CI − 0.80 to 2.54), and 95% limits of agreement was − 8.93 mmHg (95% CI − 11.81 to − 6.06) to 10.67 mmHg (95% CI 7.80–13.55) (Supplementary Information 1: Supplemental Table 1). The estimated 95% limits of agreement were almost identical, indicating that the degree of agreement between PaCO2 and EtCO2 was similar on the Y-piece side and the patient side (Fig. 4).

The square root of within-patient variance of EtCO2 was 0.65 mmHg on the Y-piece side and 1.01 mmHg on the patient side, suggesting that the repeatability of the two EtCO2 were sufficient. Histograms of differences between PaCO2 and each of the two EtCO2 measurements showed roughly normal distributions (P for normality: 0.713 for “PaCO2—patient side EtCO2” and 0.719 for “PaCO2-Y-piece side EtCO2”). Graphical inspection revealed that the variations in the differences were constant across the range of measurements (Fig. 4).

The relationship between tidal volume and difference in Y-piece side EtCO2 and patient-side EtCO2 is assessed in Supplemental Fig. 1 (Supplementary Information 1). There was no significant linear relationship [regression coefficient, − 0.001 (95% CI − 0.005 to 0.003), correlation coefficient, − 0.096].

### Table 2 Paired observations on Y-piece side and patient side of HMEF

|                      | Y-piece side | Patient side | Difference* (Y-piece side—Patient side) | P valuea |
|----------------------|--------------|--------------|-----------------------------------------|----------|
| EtCO2, (mean [SD]), mm Hg | 37.4 (5.5)   | 37.5 (6.1)   | − 0.1 (1.6)                             | 0.65     |
| Absolute difference between PaCO2 and EtCO2, (mean [SD]), mm Hg | 3.6 (3.4)    | 3.8 (3.3)    | − 0.1 (1.5)                             | 0.58     |
| Ventilator monitoring values during measurements, (mean [SD]) |              |              |                                         |          |
| Tidal volume, mL     | 418 (137)    | 431 (154)    | − 3.1 (40.7)                            | 0.64     |
| Tidal volumes adjusted on ideal body weight, mL/kgb            | 8.1 (2.1)    | 8.1 (2.3)    | − 0.03 (0.7)                            | 0.76     |
| Minute volume, L     | 6.2 (1.7)    | 6.3 (1.7)    | − 0.2 (0.6)                             | 0.10     |
| Respiratory rate/min | 17 (4.7)     | 17 (4.9)     | − 0.1 (1.2)                             | 0.79     |
| Peak pressure, cm H2O| 14.1 (5.0)   | 14.2 (4.8)   | − 0.1 (0.7)                             | 0.53     |

*HMEF, heat and moisture exchanger filter, EtCO2 end-tidal carbon dioxide, SD standard deviation
*aDifferences between paired observations
*aTwo-tailed P values of the paired samples t-test
*bIdeal body weight is computed in male as 50+[0.91×(height in centimeters − 152.4)] and in female as 45.5+[0.91×(height in centimeters − 152.4)]

**Fig. 2** Flow of patients of mechanical ventilation. HMEF, heat and moisture exchanger filter

- **Patients of mechanical ventilation in ICU**
  - Not screened (n=35)
    - Withdrawal from mechanical ventilation before screening n=35
  - Screened patients n=132
    - Ineligible (n=80)
      - Age < 20 n=19
      - Mechanical ventilation with heated humidifier n=55
      - Arterial line not inserted n=6
    - Patients with HMEF circuit and arterial line n=52
      - Excluded (n=15)
        - Pregnancy n=1
        - Patients previously enrolled in this study n=2
        - Refusal of study participation n=0
        - Patients did not satisfy the safety criteria n=4
        - Patients that treating physicians judged as inappropriate for study participation n=8
      - Included patients for analysis n=37
4 Discussion

In this prospective method comparison study, we found that the accuracy of mainstream EtCO2 measurement on the Y-piece side of HMEF was noninferior to that on the patient side. In adult ventilated patients using HMEF, our results support measuring EtCO2 with the mainstream method on the Y-piece side of HMEF.

4.1 Relation to previous studies

Our observation contrasted with previous studies, which showed that sidestream EtCO2 measurement on the Y-piece side of HMEF was lower than that on the patient side [8, 9, 22]. A study investigating 30 adult patients under general anesthesia reported that sidestream EtCO2 on the Y-piece side of the breathing filter was lower than that on the patient side by −8.85 mmHg (95% CI –19.58 to –1.95) [8]. Similar results were reported in healthy
children and critically ill adult patients [9, 22]. Several mechanisms were proposed as the reason for the lower EtCO2 values on the Y-piece side of HMEF. First, the internal volume of the HMEF serves as an additional dead space in the ventilator circuit. While exhaled gas passes through the HMEF, the dead space from the HMEF is added to the exhaled gas. This addition dilutes exhaled CO2 and thus lowers the Y-piece side of EtCO2 [7]. The impact of dilution is particularly large in patients with low tidal volumes, such as pediatric patients [7]. Second, the sidestream capnometer aspirates a large volume of gas (150–200 ml/min) from the ventilator circuit during sampling [23]. The sampled gas tends to entrain fresh gas from the ventilator circuit, resulting in dilution of exhaled CO2 [23]. The dilution of EtCO2 with fresh gas entrainment is pronounced as the sampling site becomes closer to the ventilator, that is on the Y-piece side of HMEF [24]. These dilution effects explain the lower EtCO2 values on the Y-piece side of HMEF.

In contrast, using the mainstream method, we found that the absolute difference between PaCO2 and EtCO2 was similar on both sides of the HMEF. The mainstream method of EtCO2 measurement avoids mixing with fresh gas and does not dilute exhaled CO2 during sampling. In adult patients undergoing brain surgery, mainstream EtCO2 showed better agreement with PaCO2 than sidestream EtCO2 [23]. Considering these findings, we suspected that the sidestream method with large sampling volume was a major source of error in the Y-piece side EtCO2 in previous studies [8, 9, 22]. Our study results also suggested that the dilution effect of dead space from HMEF was clinically small in adult patients with tidal volume within the observed range in this study (5–95 percentile range, 254–576 ml) [22]. Indeed, we could not find a significant relationship between tidal volume and difference in Y-piece side EtCO2 and patient side EtCO2 (Supplementary Information 1: Supplemental Fig. 1). In summary, we thought that the mainstream method and sufficient tidal volume were the main factors that maintained the accuracy of EtCO2 on the Y-piece side of the HMEF in our study.

4.2 Implications for clinicians

Placing the EtCO2 sensor on the Y-piece side of the HMEF has several advantages. HMEF prevents patients’ secretions from interfering with the EtCO2 sensors. Further, this position reduced the risk of health care workers’ exposure to unfiltered exhaled gases, during circuit disconnection or zeroing EtCO2 sensor [25]. HMEF is a cost-effective choice for humidification in situations including prolonged mechanical ventilation with less active diseases, recovering patients after elective surgery, patients without thick secretions, and cases of over-humidification with a heated humidifier [26]. Our study results suggested that patients in these situations could be safely monitored with mainstream EtCO2 on the Y-piece side of HMEF. The results of our study provide supporting evidence for current guidance on HMEF use during the coronavirus disease 2019 pandemic. (COVID 19 Anesthesia Machines and Equipment Maintenance. Anesthesia Patient Safety Foundation [6]).

Of note, in small pediatric patients, it was reported that the dead space applied by HMEF induced CO2 retention and EtCO2 monitoring on the Y-piece side of HMEF failed to detect elevated CO2 [10, 27]. Our study results should not be applied to pediatric patients. Further studies that involve HMEFs with larger dead space or patients with lower tidal volumes are needed to generalize our study results to a broader range of situations.

4.3 Strengths and weaknesses of this study

We prospectively investigated the accuracy of mainstream EtCO2 measurements. The readers of EtCO2 were unaware of PaCO2, which was the reference standard in this study. Our declaration of non-inferiority was based on an a priori defined non-inferiority margin. Our conclusion was based on the assessment of both mean difference and limits of agreement, following the reporting standards for method comparison study [20]. These features contributed to the quality of accuracy comparison in this study.

This study had several limitations. First, the included patients were selected as appropriate cases for HMEF; thus, they had relatively stable respiratory status. We selected the time of EtCO2 measurement after patients’ vital parameters were stabilized to avoid unnecessary ventilator circuit disconnection in critically ill patients. Our results were not directly applicable to patients under more severe conditions, such as extreme hypercapnia or very low tidal volume. We believe that such a severe patient is not a good candidate for the HMEF circuit. Second, the median time from HMEF placement to EtCO2 measurement was 16 h (IQR, 11–19). We could not refer to the accuracy of EtCO2 under conditions with prolonged use of HMEF, although a study showed that 120-h use of HMEFs did not increase their resistance [28]. Third, the choice of the non-inferiority margin was based on clinical judgment. However, we set a stricter margin (1 mmHg) for non-inferiority compared to a previous study (5 mmHg) [16]. Also, the non-inferiority test was conducted according to the prespecified analysis plan including sample size calculation and the pre-defined non-inferiority margin [29]. Fourth, despite prospective screening, 35 of 167 patients on mechanical ventilation could not undergo screening for the eligibility criteria. These patients required mechanical ventilation for a short period and were extubated before screening. Thus, their characteristics were considered...
to be similar to those of the study patients. We believe that excluding them from the analysis did not materially affect the study results. Fifth, we examined only one HMEF device (Hygrobag S, Medtronic), which had 45 ml of dead space. It might not be appropriate that we directly apply the study results to other HMEF devices, particularly those with larger dead space [30].

5 Conclusions

The accuracy of mainstream EtCO₂ measurements on the Y-piece side of HMEF was noninferior to that on the patient side in critically ill adult patients. Mechanically ventilated adult patients humidified with HMEF could be safely monitored with mainstream EtCO₂ on the Y-piece side of the HMEF unless their tidal volume was extremely low. This method of EtCO₂ measurement reduces sensor malfunctions and the risk of health care workers’ exposure to unfiltered gas while maintaining accuracy.

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Author contributions ST, IN, and JJ designed the study, conceptualized the data acquisition, acquired the data, and interpreted the data. ST, IN, and KG contributed to the data analysis. JJ supervised the study. IN and ST wrote the first draft of the manuscript, and all authors commented on the previous version of the manuscript. All authors read and approved the final manuscript. ST and IN have contributed equally to this work and share first authorship.

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Data availability The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest All the authors declare that they have no conflicts of interest.

Ethical approval This study was approved by the Research ethics committee of Okinawa Prefectural Chubu Hospital (2019-No.17).

Consent to participate The requirement for written informed consent was waived by the institutional review board.

Consent for publication Not applicable.

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