INTRODUCTION

It has been established that mechanical ventilation can cause diaphragm dysfunction, (ventilator-induced diaphragm dysfunction : VIDD) (1) which is associated with higher mortality in intensive care units (ICU) and hospitals (2, 3). The most important cause of VIDD and diaphragm atrophy is disuse owing to the suppression of inspiratory effort (4, 5). In animal experiments, short periods of passive controlled mechanical ventilation (CMV) has induced oxidative stress that leads to protein degradation, resulting in diaphragm-muscle atrophy and weakness (6-8). In one of the few human investigations, Levine et al. (9) reported that prolonged diaphragmatic inactivity in brain-dead organ donors was associated with marked atrophy of diaphragm myofibers. Furthermore, these detrimental effects of CMV on the diaphragm could be largely ameliorated by assist-control ventilation (ACV) (10), intermittent spontaneous breathing during CMV (11), pressure support ventilation (PSV) (12, 13), and adaptive support ventilation (14). Consequently, to preserve spontaneous effort, most critically ill patients who require mechanical ventilation receive assisted and spontaneous modalities (1, 15).

ACV is the most frequently applied mod during critical care, with 60% of mechanically ventilated patients receiving ACV (16, 17). In ACV, mechanical ventilation can be triggered by the ventilator (controlled ventilation) or the patient (assisted ventilation) (18). During controlled ventilation, triggering occurs after detection of a certain period without inspiratory effort; when this happens, diaphragm contraction does not precede the mechanical ventilation. Theoretically, the more the proportion of controlled ventilation increases during ACV, the more the diaphragm is disused. Marin-Corral et al. (19) recently observed Maastricht III organ donors who can stimulate their diaphragm donors the diaphragm completely inactive, or by comparing CMV with partially assisted mechanical ventilation. To the best of our knowledge, our clinical study is the first to investigate the effects on diaphragm atrophy, diagnosed by ultrasonography, of controlled ventilation through the course of a single ventilation mode, ACV.

We aimed to test the hypothesis that a higher proportion of controlled ventilation during the initial 48 hours of ACV would correlate with greater diaphragm atrophy among general critically ill patients.

METHODS

We conducted this study in a university hospital. Ethical approval for this study was provided by the ethics committee of Tokushima University Hospital (protocol number 3220). Written informed consent from each patient was waived as approved by the committee. This study was registered on a clinical trial (UMIN clinical trial registry : 000032944).
Study design and patients

This study is a post-hoc analysis of our prospective observational study (20) which evaluated changes in diaphragm and intercostal muscle thickness in mechanically ventilated patients. In that study, we recruited adult patients who were consecutively admitted to the ICU and expected to require mechanical ventilation for more than 48 hours. Exclusion criteria were: age under 18 years; trauma or chest tube at the measurement point; and diagnosis of primary neuromuscular disease. Among this population of the previous study, we selected patients who were on pressure-control ACV throughout at least the first 54 hours of mechanical ventilation, and also excluded patients who were continuously paralyzed with neuromuscular blocking agents.

Measurement of diaphragm thickness

In the initial study (20), on days 1, 3, 5 and 7 after the start of mechanical ventilation, we used ultrasonography to measure diaphragm thickness at peak inspiration and end-expiration (Tdi_e). Diaphragm thickening was calculated for each measurement as follows: Thickening fraction (%) = [thickness at peak inspiration – thickness at end-expiration] / thickness at end-expiration] × 100. Data collection was discontinued, whichever occurs first, at extubation, at patient discharge from the ICU, or at death. Measurement procedures are fully detailed in our previous study. In brief, referring to previously reported methods, measurement was performed using B mode ultrasound with the linear transducer perpendicularly placed on the right chest wall at the zone of apposition (21). Of note, each recording was performed by the same investigator and actual measurement of diaphragm thickness was retrospectively done by the same investigator with the stored images in order to blind the data analysis from each patient’s status.

Proportion of controlled ventilation

Reviewing patient charts, we retrospectively calculated the proportions of controlled ventilation and assisted ventilation during the initial 48 hours of ACV. To eliminate the possible effects of neuromuscular blocking agents that might have been used during tracheal intubation or in the operating theater, we focused on the 48-hour-period starting 6 hours after the start of mechanical ventilation in the ICU. That is why inclusion criteria required ICU patients who were on ACV for more than 54 hours. Actual respiratory frequency is automatically recorded by the minute in our electrical system (PrimeGaia, Nihon Kohden, Tokyo, Japan). Set values for respiratory rate were manually entered into the same system by bedside nurses. While actual respiratory frequency was equal to the set value for respiratory rate, we assumed that mechanical breaths delivered in the minute were all controlled ventilation triggered by the time. While actual respiratory frequency was greater than the set value for respiratory rate, mechanical breaths delivered in the minute were all considered as assisted ventilation triggered by the patient. Then, we calculated the proportion of controlled ventilation during the initial 48 hours of ACV (CV%a) according to the formula: CV%a (%) = [total minutes of controlled ventilation/48 × 60] × 100.

Endpoints of the study

The primary endpoints of this study were the direction and maximum variation in Tdi_e during mechanical ventilation. According to median CV%a , we assigned patients to either of two groups and performed intergroup comparison of direction and maximum variation in Tdi_e. Secondary endpoints were duration of mechanical ventilation, incidence of reintubation and tracheostomy, and ICU mortality.

Clinical data collection

Demographic data, APACHE (acute physiology and chronic health evaluation) II score on admission to the ICU, reason for mechanical ventilation and clinical outcomes were gathered from medical charts. Then, for the initial 48-hour period of ACV, we collected the following physiological and ventilator variables: set values for respiratory rate; actual respiratory frequency; plateau pressure; positive end-expiratory pressure (PEEP); tidal volume; and arterial blood gas analysis.

Statistical analysis

Continuous data are presented as medians with interquartile range (IQR), whereas categorical variables are expressed as numbers and percentages. Direction of changes in Tdi_e over time were analyzed in each group by repeated measures of analysis of variance with multiple comparisons to reveal effects over time. Differences between continuous variables, that is maximum variation in Tdi_e, thickening fraction, ventilatory and physiological variables, and duration of mechanical ventilation were assessed using t tests or Mann-Whitney U tests. Categorical variables, that is, incidence of reintubation, tracheostomy, and death in the ICU, were assessed as appropriate with chi-squared tests or Fisher exact tests. Statistical calculations were carried out with statistics software (SPSS, version 26, SPSS Inc., Chicago, IL). P < 0.05 was considered statistically significant.

RESULTS

From the 80 patients in the preliminary study, we selected the 64 patients who were on pressure-control ACV throughout at least the first 54 hours of mechanical ventilation. We then excluded 8 patients who had been continuously paralyzed with neuromuscular blocking agents, and finally analyzed valid data from 56 patients (Fig. 1). Assessing median CV%a as 24.9%, we assigned patients to either of two groups: Low group, CV%a less than 25%; High group, CV%a more-than-or-equal-to 25%. Table 1 shows the characteristics of the Low and High groups. The most frequent reason for mechanical ventilation was acute respiratory failure (34%) for Low group and post-operative care (30%) for High group.

![Flow chart of study participants](Image 300x118 to 538x289)
Diaphragm thickness was measured in 100%, 100%, 73% and 43% of patients on days 1, 3, 5 and 7, respectively. $T_{di}^{ee}$ was 2.1 mm [IQR, 1.6 to 2.5], 1.9 mm [IQR, 1.5 to 2.5], 1.8 mm [IQR, 1.6 to 2.5] and 2.0 mm [IQR, 1.4 to 2.7], and thickening fraction was 8.3% [IQR, 4.0 to 17.1], 8.3% [IQR, 4.9 to 12.4], 6.9% [IQR, 3.2 to 16.2] and 5.6% [IQR, 0.0 to 10.6] on days 1, 3, 5 and 7, respectively. $T_{di}^{ee}$ increased by more than 10% from the baseline in 6 patients (11%), unchanged without a 10% increase or decrease in 8 patients (14%) and decreased by more than 10% in 42 patients (75%). Primary and secondary outcomes are summarized in Fig. 2 and Table 2. Over the first week of mechanical ventilation, $T_{di}^{ee}$ decreased in both Low group (difference, -7.4%; 95% confidence interval [CI], -10.1% to -4.6%; p < 0.001) and High group (difference, -5.2%; 95% CI, -8.5% to -2.0%; p = 0.049) (Fig. 2). Maximum variation in $T_{di}^{ee}$ from the baseline showed no intergroup difference (Low, -15.8% [IQR, -22.3 to -1.5] vs. High, -16.7% [IQR, -22.6 to -11.1], p = 0.676). There was no statistically significant intergroup difference in duration of mechanical ventilation, incidence of reintubation and tracheostomy, and ICU mortality (Table 2).

Table 1. Patient characteristics

|                | Low group (N=29) | High group (N=27) | P       |
|----------------|------------------|-------------------|---------|
| Age, yr        | 74 (63–80)       | 66 (5–73)         | 0.049   |
| Male, n (%)    | 18 (62)          | 17 (63)           |         |
| Height, cm     | 158 (155–163)    | 160 (152–170)     |         |
| Weight, kg     | 58 (48–69)       | 61 (51–69)        |         |
| APACHE II score| 27 (21–32)       | 22 (15–28)        |         |
| Reason for mechanical ventilation, n (%) | | | |
| Acute respiratory failure | 10 (34) | 4 (15) |         |
| Stroke         | 5 (17)           | 2 (7)             |         |
| Post CPR       | 4 (14)           | 3 (11)            |         |
| Post-operative care | 4 (14) | 8 (30) |         |
| Sepsis/Septic shock | 3 (10) | 4 (15) |         |
| Acute heart failure | 2 (7) | 4 (15) |         |
| Others         | 1 (4)            | 2 (7)             |         |

Data are expressed as median (interquartile range). APACHE, acute physiology and chronic health evaluation; CPR, cardio-pulmonary resuscitation.

Table 2. Primary and secondary outcomes

| Variables                          | Low group (N=29) | High group (N=27) | P      |
|------------------------------------|------------------|-------------------|--------|
| **Primary outcome**                |                  |                   |        |
| Maximum variation in $T_{di}^{ee}$% | -15.8 (-22.3 to -1.5) | -16.7 (-22.6 to -11.1) | 0.676  |
| **Secondary outcome**              |                  |                   |        |
| Duration of MV, hour               | 254.3 (88.0–216.5) | 303.5 (105.5–513.5) | 0.145  |
| Reintubation, n (%)                | 3 (10.3)         | 2 (7.4)           | 0.767  |
| Tracheostomy, n (%)                | 7 (24.1)         | 6 (22.2)          | 0.991  |
| ICU mortality, n (%)               | 7 (24.1)         | 5 (18.5)          | 0.715  |

Data are expressed as median (interquartile range) unless otherwise noted. $T_{di}^{ee}$, end-expiratory diaphragm thickness; MV, mechanical ventilation; ICU, intensive care unit.
Table 3. Ventilation and physiological variables during the initial 48-hour period of assist-controlled ventilation

| Variables                         | Low group (N = 29)          | High group (N = 27)          | P     |
|----------------------------------|-----------------------------|------------------------------|-------|
| Set respiratory rate, per min    | 13.6 (12.2 – 15.1)          | 16.4 (14.4 – 18.9)          | 0.003 |
| Actual respiratory frequency, per min | 18.7 (18.1 – 21.4)      | 17.7 (16.3 – 20.5)         | 0.245 |
| CV48%, %                         | 5.1 (1.6 – 13.7)           | 53.8 (36.4 – 61.6)         | <0.001|
| Peak pressure, cm H2O            | 19.5 (17.4 – 21.9)         | 21.5 (19.0 – 23.2)         | 0.026 |
| Plateau pressure, cm H2O         | 18.9 (16.7 – 21.4)         | 21.1 (18.9 – 22.7)         | 0.017 |
| Positive end-expiratory pressure, cm H2O | 7.8 (6.0 – 8.4) | 8.0 (7.2 – 11.0)         | 0.030 |
| Tidal volume, mL per kg PBW      | 9.1 (7.7 – 10.1)           | 7.8 (7.1 – 8.8)            | 0.029 |
| FIO2, %                          | 32 (25 – 39)               | 39 (29 – 51)               | 0.184 |

Arterial blood gas analysis:

| Variable            | Low group (N = 29) | High group (N = 27) | P     |
|---------------------|--------------------|---------------------|-------|
| pH                  | 7.44 (7.41 – 7.47) | 7.41 (7.34 – 7.43)  | 0.003 |
| PaCO2, mm Hg        | 35.3 (31.2 – 39.3) | 40.4 (35.7 – 46.2)  | 0.352 |
| PaO2, mm Hg         | 88.1 (75.5 – 92.9) | 91.5 (81.7 – 101.6) | 0.220 |
| PaO2/FIO2, mm Hg    | 269 (206 – 366)    | 269 (153 – 340)    | 0.533 |
| Thickening fraction, %| 12.5 (8.3 – 22.5) | 17.4 (11.1 – 22.2) | 0.367 |

Data are expressed as median (interquartile range). CV48% represents the proportion of controlled ventilation for the initial 48 hours of assist-control ventilation. CV, controlled ventilation; PBW, predicted body weight.

DISCUSSION

This study revealed four important findings. (1) Contrary to our hypothesis, Tdi of the Low group decreased over time in both groups but no maximum variation in Tdi of the Low group was associated with high proportion of controlled ventilation during early-phase of ACV. (2) Higher proportion of controlled ventilation during ACV was associated with lower set value for respiratory rate. (3) Despite higher plateau pressure and PEEP, tidal volume was significantly less in the High group than in the Low group. (4) There was no significant intergroup difference in clinical outcomes.

The best established causal evidence for diaphragm myotrauma is disuse atrophy (4, 5). Consequently, we focused on diaphragm inactivity during ACV, which is sometimes overlooked because respiratory muscle monitoring is not standard in most ICUs (22), and because every delivered breath during ACV looks similar to quiet breathing at rest. To do this, it is necessary to optimize ventilation settings and sedation level (25) and thus control neural respiratory drive.

In this study, Low group showed higher tidal volume in spite of lower driving pressure (plateau pressure minus PEEP). Because there was no intergroup difference in thickening fraction, Low group might have more of compliant lungs than increased inspiratory efforts. This was seen as one reason for lower tidal volume and higher PEEP in High group. In a recent animal study (26), lung protective ventilation with low tidal volume and high PEEP worsened VIDD by inducing oxidative stress and succeeding downregulation of peroxisome proliferator-activated receptor γ coactivator 1alpha (PGC-1α), reactive oxygen species inhibitor in diaphragm. This result is consistent with another study (27) showing that mechanical ventilation with a very large tidal volume of 35 mL/kg results in less oxidative stress in the diaphragm than ventilation with a moderate tidal volume of 9 mL/kg. Although the relationship between high PEEP and oxidative stress is unknown, excessive PEEP is associated with a rapid reduction in the number of sarcomeres and the partially assisted ventilation. In one of these studies (15), contractile activity decreased according to the number of days of controlled modes of ventilation. Moreover, in patients receiving controlled modes of ventilation, contractile activity was slightly but significantly greater if respiratory frequency was higher than the set rate. Even in PSV, high pressure levels of prolonged PSV developed diaphragm atrophy and contractile dysfunction (23). Such results suggested that presence of triggering, or occurrence of diaphragm activity in itself may not be sufficient to prevent diaphragm atrophy. Moreover, the protective effect of diaphragm contraction seems to depend on the amount of inspiratory effort. Actually, we did not observe significant intergroup differences in inspiratory efforts represented by the thickening fraction. While we remain unsure what level of inspiratory effort is optimal, results from other investigations (3, 14, 24) suggest that the most effective approach may be to keep inspiratory effort similar to quiet breathing at rest. To do this, it is necessary to optimize ventilation settings and sedation level (25) and thus control neural respiratory drive.
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