Journal of Critical Care 45 (2018) 105–109

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Effect of hypercapnia on respiratory and peripheral skeletal muscle loss during critical illness – A pilot study

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1. Introduction

It is well recognised that critical illness contributes to development of muscle weakness (ICU-AW) [1] with evidence that atrophy is caused by increased breakdown and decreased synthesis of muscle protein [2-5]. This may be secondary to inflammation, immobilisation, changes in endocrine stress responses, nutritional deficit and denervation, yet none of the above show direct correlation with ICU-AW [5].

Skeletal muscle loss occurs early and rapidly during the first week of critical illness and is more severe among those with multi-organ failure compared with single organ failure [6]. For critically ill patients with Acute Respiratory Distress Syndrome (ARDS) muscle weakness is the single greatest determinant of functional outcome [6]; the weakness impeding rehabilitation and recovery due to prolonged inactivity, a catabolic state and reduced nutritional uptake [7]. Similarly, impaired diaphragm contractility has profound long-term sequelae resulting in prolonged periods of mechanical ventilation, delayed weaning and potential ongoing respiratory compromise [8].

Low tidal volume (LTV) ventilation is associated with a reduced risk for developing ventilator induced lung injury with or without ARDS [9]. Meta-analyses have demonstrated fewer pulmonary infections, less atelectasis and shorter length of stay with targeted lung volumes [10]. As such, LTV ventilation or 'lung protective ventilation' has become common place in critical care [11]. However, an accepted side-effect of LTV is 'permissive' hypercapnia.

Little is known about the influence of hypercapnia on muscle wasting in humans but animal models have shown that severe acute acidosis can protect the contractility of the diaphragm [12]. A recent study using a healthy animal model demonstrated that moderate prolonged hypercapnia (defined as $PaCO_2$ between 7.3 kPa and 9.3 kPa for 72 h) protected against ventilator induced diaphragmatic dysfunction (VIDD) [12], this is possibly as a consequence of an anti-inflammatory effect mediated by preventing oxidative stress and NF-kappa B activation [13-15]. It remains unknown if this effect occurs in humans, and whether hypercapnia could prevent both diaphragmatic and peripheral skeletal muscle wasting in critically ill patients.

The aim of this pilot study was therefore to investigate the effect of hypercapnia on changes in respiratory and peripheral skeletal muscle in critically ill patients receiving mechanical ventilation.

2. Methods

2.1. Study design

A prospective observational pilot study to measure change in respiratory muscle (diaphragm) thickness and peripheral skeletal muscle (quadriceps rectus femoris cross-sectional area (RF_{CSA})) in three non-matched groups of invasively mechanically ventilated patients with differing levels of arterial carbon dioxide.

2.2. Ethical approval

Ethical approval was obtained from Wales Research Ethics Committee – REC3 (14/WA/0054). Written informed consent was provided directly from patients or their personal consultee (with retrospective patient consent obtained once capacity restored).

2.3. Participants

Adult (≥18 years of age) patients admitted to a 32-bedded tertiary referral critical care unit and receiving a mandatory mode of invasive mechanical ventilation, were eligible for the study.

Two groups of patients were initially identified with a further retrospective grouping of patients during analysis. Group 1 consisted of patients admitted with acute brain injury (ABI). This group was included as patients with brain injury normally ventilated to a $PaCO_2$ 4.5–5.0 kPa and on similar medication to those admitted with severe respiratory failure (e.g. sedation, use of paralysing agents). The remaining included patients had no diagnosis of head injury. At the end of the study this group of nonhead injury patients were retrospectively categorised into 'Normocapnic' [Group 2] ($PaCO_2$ 4.6–5.9 kPa) or 'Hypercapnic' [Group 3] (≥6 kpa) groups according to average $PaCO_2$ during the study period (calculated from daily blood gases).

Exclusion criteria included expected deterioration leading to death within 24 h, pre-existing muscle or neuromuscular disease, or chronic respiratory disease.

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https://doi.org/10.1016/j.jcrc.2018.02.002
0883-9441/

2.4. Sample size

No previous studies provided sufficient data for a sample size calculation to be carried out. A convenience sample of 30 was used to ensure 10 participants in each group. This was deemed feasible within the funding period of the study.

2.5. Protocol

Ultrasonographic measurements of RF_{CSA} and diaphragm thickness were completed using a Sonosite X-Porte© ultrasound device (Fujifilm™) based on previously described techniques [5,7,16]. Subjects were positioned semi-supine with the legs rested in passive extension. Use of excess ultrasound gel facilitated image quality, and the visual feedback was used to obtain the smallest cross-sectional area/diaphragm thickness in each image. Minimal compression was applied to avoid compression of the underlying muscle.

Measurements of RF_{CSA} and diaphragm thickness commenced within the first 24 h of initiation of mechanical ventilation (classified as 'baseline'), and were repeated on Days 3, 5, 7, and 10 or until discontinuation of mechanical ventilation (whichever occurred first).

For the diaphragm, a 13–6 MHz rectangular transducer (L25xp, Sonosite S Series Ultrasound, Hitchin, UK) was placed in the right mid-auxiliary line between the 8th and 9th rib. Confirmation of imaging the diaphragm was made through direct visualisation of a contraction or passive stretching. All images were obtained at end-expiration.

RF_{CSA} was determined using a 5–2 MHz curvilinear transducer (C60xp, Sonosite S Series Ultrasound, Hitchin, UK). Distance from the anterior superior iliac spine (ASIS) to the superior patellar border was measured and a point marked on the thigh, at two-thirds of this distance. The transducer was placed perpendicular to the long axis of the thigh on the superior aspect.

Ultrasound images were analysed using Image J software (Image J, U.S. National Institutes of Health, Maryland USA, http://rsb.info.nih.gov/ij/). For both the diaphragm and RF_{CSA}, three images were obtained at each time point.An average of three measurements (all within a 10% variance) was calculated from each image and then an overall average was then calculated for the three images captured at each time point to provide a single figure for diaphragm thickness and RFcsa.

2.6. Statistical analysis

Demographic data was analysed using descriptive statistics. Inter-group baseline differences were analysed using either one-way anova with poc hoc Bonferroni tests or Kruskall-Wallis for non-parametric data.

Changes in diaphragm thickness and RFcsa were calculated by percentage change from baseline (within 24 h of initiating mechanical ventilation) to each subsequent assessment point (Days 3, 5, 7 and 10). To assess the degree of change in muscle thickness/cross sectional area, all data were assessed for normality using histograms. Descriptive analysis included mean and standard deviations, followed by multilevel linear regression analysis, accounting for the correlated nature of repeated measurements within individuals. Pearson's correlation was used to assess correlation between relative change in RF_{CSA} and diaphragm thickness at each time point during mechanical ventilation.

Statistical analysis was completed using SPSS© Version 20 (SPSS, Inc. Chicago, Ill) and Stata Version 13.0. A p-value of ≤0.05 was considered statistically significant.

3. Results

3.1. Participants

Twenty-six patients were recruited between April and November 2014, of which 9 were categorised as Group 1, 7 as Group 2 and 10 as Group 3. Baseline characteristics for the patients according to group are reported in Table 1. As expected inter-group analysis demonstrated significant variation in average partial pressure of carbon dioxide ($p = 0.000$), with the hypercapnic group having significantly higher levels. The hypercapnic group also had significantly higher APACHE II scores ($F = 4.410$; $p = 0.024$, post hoc group 1 & 3 $p = 0.022$), and lower numbers of organs failing on admission ($H = 15.030$; $p = 0.001$) when compared to both the normocapnic ($U = 17.000$; $p = 0.037$) and acquired brain injury groups ($U = 4.000$; $p < 0.001$). All other inter-group baseline differences were non-significant.

3.2. Changes in diaphragm thickness

Differences from baseline for the whole cohort ($n = 26$) were: day 3–0.44% (9.0) $n = 25$; day 5–2.3% (7.9) $n = 22$; day 7–5.8% (9.5) $n = 17$; and day 10–6.5% (6.7) $n = 7$ (see Fig. 1). Significant differences were observed between baseline to day 7 ($p = 0.029$) and baseline to day 10 ($p < 0.001$). Inter-group comparisons for diaphragm thickness were non-significant at each time point ($p = 0.132$) (see Table 2).

3.3. Changes in RF_{CSA}

Change in RF_{CSA} from baseline to Days 3, 5, 7, and 10 was calculated for all patients (Fig. 2). Day 3 mean change from baseline was −4.0% (3.3) $n = 25$; day 5–7.0% (4.1) $n = 22$; day 7–10.5% (5.4) $n = 17$; and day 10–14.9% (8.2) $n = 8$. Significant differences ($p < 0.001$) were observed for all comparisons from baseline (baseline to day 3, 5, 7, and 10). Inter-group analysis showed no significant differences between the groups ($p = 0.211$) (Table 3).

3.4. Relationship between change in diaphragm thickness and RF cross-sectional area

The relationship between percentage change in diaphragm thickness and RF_{CSA} at all time points was analysed using bivariate Pearson product-moment correlation coefficient and was not statistically significant (day 3: $r = -0.161$; day 5: $r = -0.099$; day 7: $r = 0.002$; day 10: $r = 0.088$).

4. Discussion

This study demonstrated a significant decline in RF_{CSA} from baseline to days 3, 5, 7 and 10 and in diaphragm thickness from baseline to days 7 and 10. There were no differences between the groups in either outcome measure, indicating that hypercapnia did not appear to influence respiratory and peripheral skeletal cross-sectional area in this small sample of people who were critically ill and receiving mechanical ventilation.

4.1. Change in diaphragm muscle mass

In the cohort of patients recruited, there was an average decrease of approximately 6% in diaphragm thickness by day 10 (from baseline). This decrease was significant at day 7 when compared to baseline ($p = 0.029$).

The observed reduction in diaphragmatic thickness was substantially less than that reported by both Grosu et al. [16] (6% per day of mechanical ventilation) and Schepens et al. [17] (26% change from baseline at 72 h). However, recently Goligher et al. [18] examined changes in diaphragmatic thickness in a large multicentre cohort of 107 mechanically ventilated and 10 non-ventilated critically ill patients. In this cohort, there was a reduction of >10% thickness in 44% of patients, unchanged (<10%) in 44% of patients and increased (>10%) in 12% of patients. Similarly, Zambon et al. [19] identified that rate of diaphragm thickness change was dependent on the mode of ventilation being delivered, with mandatory modes causing 7.5% loss of thickness after 3 days,