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The metabolic cost of inspiratory muscle training in mechanically ventilated patients in critical care

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Abstract

Background: Diaphragmatic dysfunction is well documented in patients receiving mechanical ventilation. Inspiratory muscle training (IMT) has been used to facilitate weaning by strengthening the inspiratory muscles, yet the optimal approach remains uncertain. Whilst some data on the metabolic response to whole body exercise in critical care exist, the metabolic response to IMT in critical care is yet to be investigated. This study aimed to quantify the metabolic response to IMT in critical care and its relationship to physiological variables.

Methods: We conducted a prospective observational study on mechanically ventilated patients ventilated for $\geq$ 72 h and able to participate in IMT in a medical, surgical, and cardiothoracic intensive care unit. 76 measurements were taken on 26 patients performing IMT using an inspiratory threshold loading device at 4 cmH_2O, and at 30, 50 and 80% of their negative inspiratory force (NIF). Oxygen consumption (VO_2) was measured continuously using indirect calorimetry.

Results: First session mean (SD) VO_2 was 276 (86) ml/min at baseline, significantly increasing to 321 (93) ml/min, 333 (92) ml/min, 351(101) ml/min and 388 (98) ml/min after IMT at 4 cmH_2O and 30, 50 and 80% NIF, respectively ($p = 0.003$). Post hoc comparisons revealed significant differences in VO_2 between baseline and 50% NIF and baseline and 80% NIF ($p = 0.048$ and $p = 0.001$, respectively). VO_2 increased by 9.3 ml/min for every 1 cmH_2O increase in inspiratory load from IMT. Every increase in P/F ratio of 1 decreased the intercept VO_2 by 0.41 ml/min (CI — 0.58 to — 0.24 $p < 0.001$). NIF had a significant effect on the intercept and slope, with every 1 cmH_2O increase in NIF increasing intercept VO_2 by 3.28 ml/min (CI 1.98–4.59 $p < 0.001$) and decreasing the dose–response slope by 0.15 ml/min/cmH_2O (CI — 0.24 to — 0.05 $p = 0.002$).

Conclusions: IMT causes a significant load-dependent increase in VO_2. P/F ratio and NIF impact baseline VO_2. The dose–response relationship of the applied respiratory load during IMT is modulated by respiratory strength. These data may offer a novel approach to prescription of IMT.

Take home message: The optimal approach to IMT in ICU is uncertain; we measured VO_2 at different applied respiratory loads to assess whether VO_2 increased proportionally with load and found VO_2 increased by 9.3 ml/min for every 1 cmH_2O increase in

inspiratory load from IMT. Baseline NIF has a significant effect on the intercept and slope, participants with a higher baseline NIF have a higher resting VO_2 but a less pronounced increase in VO_2 as the inspiratory load increases; this may offer a novel approach to IMT prescription.

Background

Critically ill patients undergoing mechanical ventilation (MV) commonly develop significant diaphragmatic dysfunction. Diaphragmatic atrophy occurs rapidly after initiation of MV [1] with reductions of up to 10% in diaphragm thickness reported within 4 days [2]. Diaphragm dysfunction is present in 63–80% of patients mechanically ventilated for over 48 h [3, 4] and continues after liberation from MV [5].

Diaphragmatic dysfunction is associated with weaning failure [3], delayed extubation [6], increased mortality and readmission to the Intensive Care Unit (ICU) [7, 8] and increased risk of ventilator-associated complications [2]. Low baseline diaphragmatic mass is associated with delayed liberation from ventilation, a higher risk of complications and increased risk of hospital death [5, 9].

Physical rehabilitation strategies have long been used to improve physical function in intensive care, frequently focussing on lower limb strength. Little attention has been given to specific interventions to enhance strength of the respiratory muscles in intensive care patients until relatively recently [10].

Inspiratory muscle training (IMT) targets the diaphragm, intercostals and accessory inspiratory muscles with the goal of improving muscle strength and endurance through the application of controlled threshold resistance or adjusting trigger sensitivity during inspiration [11, 12]. Although not used widely, sufficient clinical data exist to support the continued study of IMT in patients in critical care, significantly improving maximal inspiratory pressure [12]. Preliminary data show IMT can improve the likelihood of weaning success, but this needs further confirmation owing to differing training regimes and methodological heterogeneity of current literature [12].

The optimal approach to IMT remains uncertain [12]. Training regimes vary widely across the literature and include high-intensity threshold interval training where the patient performs a set number of breaths and sets, or endurance focussed training lasting 5–30 min by adjusting ventilator trigger sensitivity. Protocols vary greatly with resistance levels set anywhere between 20 and 50% of the patient's initial inspiratory strength or the maximum resistance tolerable by the patient [13, 14].

Loaded resistive breathing in healthy participants found that oxygen consumption (VO_2) closely correlated with time to respiratory muscle fatigue [15]. The metabolic demands of exercise are poorly understood in the ICU setting [16], and whilst some data on metabolic response to whole body exercise in critical care exist [17–19], the

metabolic response to IMT in critical care is yet to be investigated; such data could provide insight into the optimal IMT prescription in critical care.

The purpose of this observational study was to measure the oxygen consumption of mechanically ventilated patients at rest and at increasing levels of IMT resistance. The relationship between VO_2, respiratory strength, and other physiological variables was also investigated.

Methods

Participants

The study was a single-centre observational study performed across two cardiothoracic intensive care units within Guy's and St Thomas' NHS Foundation Trust, London, UK between October 2021 and May 2022.

The study protocol was approved by the local research and development department, the Wales research ethics committee 4 (Reference 21/WA/0268) on 14th September 2021, and the Health Research Authority on 15th September 2021. The study is registered on ClinicalTrials.gov, registration number: NCT05101850. The study was conducted according to the Declaration of Helsinki as most recently amended and Good Clinical Practice standards.

Participants were included if they were aged 18 years or over, had been invasively ventilated for ≥ 72 h with an endotracheal tube or tracheostomy in situ, respiratory rate of ≤ 35 breaths/min, fraction of inspired oxygen (FiO_2) ≤ 0.50, co-operative and able to participate in inspiratory muscle training, and if they or their representative gave informed consent / surrogate approval. Exclusion criteria were an undrained pneumothorax/pneumomediastinum, extracorporeal membrane oxygenation (ECMO), the absence of an arterial catheter for blood sampling, pregnancy, being considered unlikely to survive, or consultant discretion that the patient was not otherwise appropriate.

Inspiratory muscle training

Inspiratory muscle training was performed in-line with the ventilator circuit to allow accurate VO_2 and carbon dioxide production (VCO_2) measurement as most participants were also receiving supplemental oxygen when studied. Figure 1 details connection of
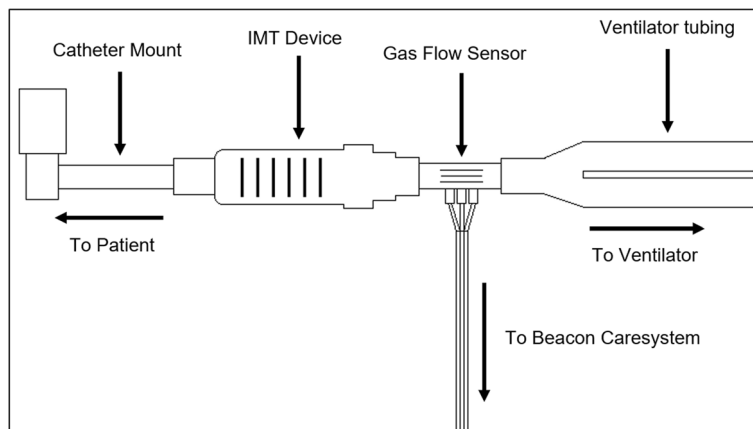

Fig. 1 Connection of the IMT device and indirect calorimetry flow sensor into the ventilator circuit

the IMT device and indirect calorimetry flow sensor into the ventilator circuit. A Philips Respironics® Threshold IMT device HS730010 or Philips Respironics® Threshold positive expiratory pressure (PEP) device HS735010 was used for IMT. The Threshold PEP device is marketed as an expiratory positive pressure device but can provide an inspiratory threshold load in the exact same fashion as the IMT device if the patient inspires through the exhalation port as previously described [14], which allowed patients with a low negative inspiratory force (NIF) to train.

A high-intensity IMT approach as described by Bissett et al. (2018) and other studies [11, 14] was used. Before the initiation of each set, ventilatory pressure support was set at 0 cmH_2O. The participant was instructed to initiate breaths from functional residual capacity and encouraged by the investigator to inhale deeply against the resistance 6 times at their own pace; no set breathing frequency was imposed. After 6 breaths, the patient rested on their baseline ventilation for approximately 30 s and then performed 6 further breaths. Participants performed two sets of six breaths at 4 cmH_2O resistance and at 30, 50 and 80% of their NIF. To allow for recovery, patients rested for 10 min between each IMT load on their baseline ventilation.

Participants were studied up to four days per week until they were successfully extubated, decannulated from their tracheostomy, weaned from assisted mechanical ventilation, repatriated to a non-participating site or ceased to obey commands. Additional file 1: Appendix A details reasons for discontinuation of study data collection.

Measurement of VO_2 and VCO_2

The Beacon Caresystem (Mermaid care A/S, Norresundby, Denmark) is a bedside decision support system using mathematical models powered by an individual patient's physiology to advise on appropriate ventilator settings. The Beacon Caresystem's breath by breath indirect calorimetry function was used to measure VO_2 and VCO_2 in this study. The device can reliably measure VO_2 and VCO_2 at 0.21–0.85 FiO_2 and has shown agreement when measuring VO_2 and VCO_2 at 21% and 50% inspired oxygen with the E-sCOVX® (GE healthcare, Helsinki, Finland) [20] and accurate compared to the QUARK RMR (COSMED, Rome, Italy) [21] indirect calorimetry devices.

The Beacon Caresystem was connected to the participant by inserting a standard respiratory gas flow sensor (SPIRT™ flow sensor, Adult. Artema Technology, Germany) into the ventilator circuit, close to the patient's airway 20-min before initiation of IMT. Baseline VO_2 was measured as a 2-min average during a steady state of rest with the participant on their normal ventilatory support.

Pilot observations showed that the VO_2 and VCO_2 signal was distorted by the high resistance of the IMT device, and frequently by lower tidal volumes associated with IMT. The applied inspiratory load caused an oxygen deficit after training, as described in previous work where post exercise oxygen consumption reflected the level of anaerobic metabolism in previous peripheral muscle resistance exercise [22]. For this reason, IMT VO_2 was analysed as a 2-min average immediately after each applied respiratory load. Figure 2 shows a typical full protocol of IMT with the VO_2 and VCO_2 signal output from the Beacon Caresystem.

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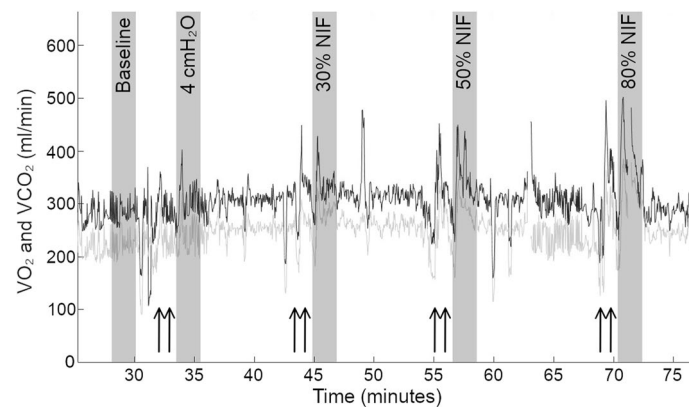
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Fig. 2 A typical participant's VO_2 / VCO_2 flow signal. Black line shows VO_2 signal, grey line shows VCO_2 signal. Shaded grey area shows 2-min average taken at baseline and after each training load. Black arrows show IMT training periods

Measurement of negative inspiratory force

NIF was measured on day 0 and every 5–7 days (for details see Additional File 1: Appendix B).

Measurement of pulmonary shunt

To investigate whether IMT affects pulmonary gas exchange, pulmonary shunt was estimated prior to and after IMT. This was measured using a procedure that varies inspired oxygen fraction, a feature of the Beacon Caresystem [23].

Statistical analysis

Data are presented as mean (SD) or median (interquartile range). Data were tested for normality using Kolmogorov–Smirnov and Shapiro–Wilk tests. First session VO_2 levels following each IMT dose were compared using one-way ANOVA with Tukey's correction for multiple post hoc comparisons. The dose–VO_2 response relationship, and the influence of baseline factors, were evaluated using linear mixed effects modelling. Data from 51 IMT sessions across all 26 patients were included into the linear mixed model (LMM) analysis. There was a range of 1–4 sessions included from individual patients. LMM accounts for differing contributions from individual participants, hence the analysis is not weighted in favour of contributions from those patients who contributed more data. A paired T-test was used to analyse change in pulmonary shunt. A two-tailed level of $p < 0.05$ was considered statistically significant. Statistical analyses were performed by SPSS Version 28 for Windows (IBM, Inc., Chicago, IL).

Results

Recruitment

The flow of participants is presented in Fig. 3. 29 participants were recruited to the study; two participants withdrew during the first IMT set due to increased work of breathing, and measurements were ceased in one participant as their respiratory rate increased to over 35 breaths/min after connection to the IMT device. 76
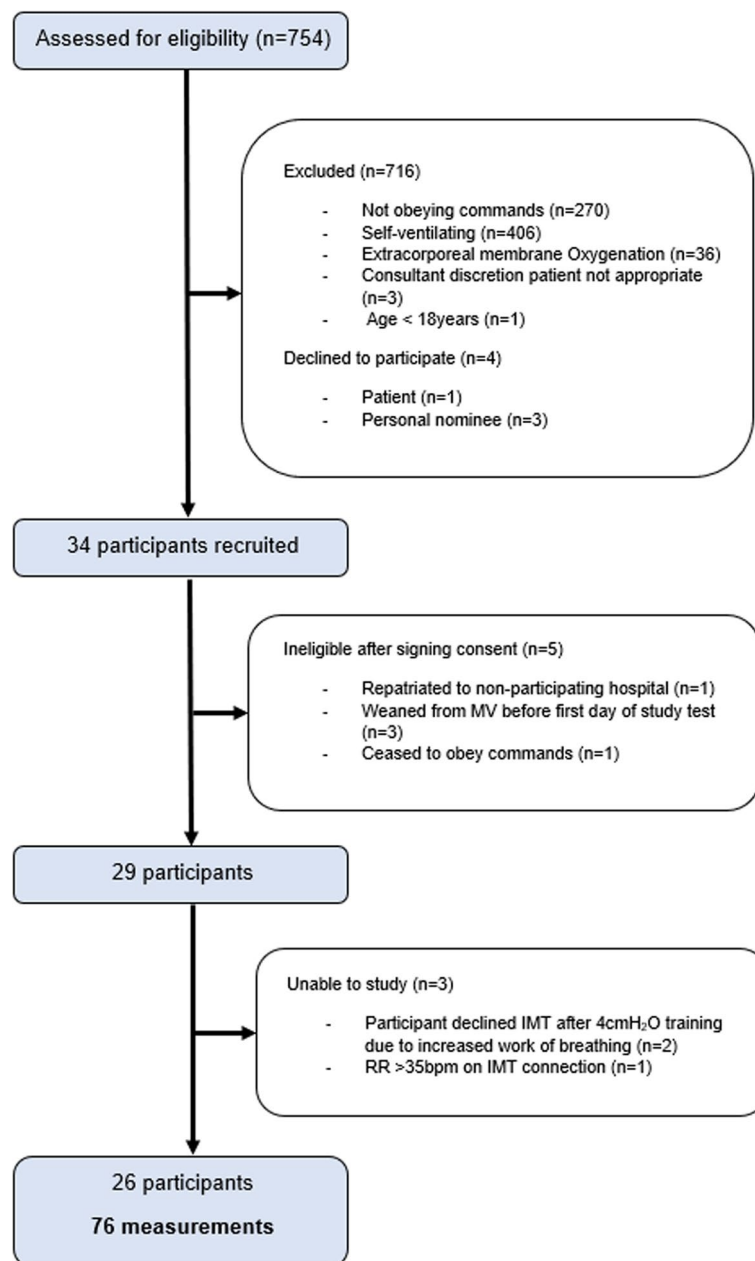
Fig. 3 Flow of participants

measurements were performed in 26 participants. Main characteristics and physiological values of patients are presented in Table 1; detailed patient diagnoses are provided in Additional File 1: Appendix C.

Effect of IMT resistance on oxygen consumption

Main VO_2 results are presented as ml/min; IMT loads the respiratory muscles only, therefore measured oxygen consumption has a limited relationship to body weight. ml/kg/min are presented for reference purposes and comparison with other studies.

Table 1 Baseline demographic and physiological characteristics

Variables	$n = 26$
Sex, male:female	20:6
Age (years)	54.3 (14.5)
Estimated body weight (kg)	88.2 (27.7)
BMI (kg/m^2)	27.3 (23.1–33.4)
Length of mechanical ventilation prior to IMT (days)	18.0 (11.8–25.2)
Length of stay (ICU) prior to IMT (days)	21.0 (12.7–28.5)
APACHE 2 score (admission)	25.8 (8.1)
SOFA score	7.0 (6.8–10.0)
NIF (cmH$_2$O)	32 (22.6–39.3)
CRP	50 (20.5–75.5)
P/F ratio (mmHg)	267.3 (75.0)
FiO$_2$	0.35 (0.08)
PaO$_2$ (mmHg)	88.4 (13.2)
P0.1 (cmH$_2$O)	− 1.3 (− 3.4 to − 1.3)
Pressure support (cmH$_2$O)	11.6 (5.2)
Positive end expiratory pressure (PEEP) (cmH$_2$O)	7.3 (2.2)
Vasopressor Inotrope Score	0.0 (0.0–4.0)
Barthel index	20 (20–20)

Data presented as mean (SD) or median (25th centile–75th centile), unless otherwise indicated. APACHE II = Acute Physiology and Chronic Evaluation Score. SOFA = Sepsis Organ Failure Score

Table 2 Effect of IMT on oxygen consumption and respiratory quotient (first session)

	Baseline $N = 26$	4 cmH$_2$O $N = 26$	30% NIF $N = 26$	50% NIF $N = 24$	80% NIF $N = 19$	*p* value
VO$_2$ (ml/min)	276 (86)	321 (93)	333 (92)	351 (101)	388 (98)	0.003
VO$_2$ (ml/kg/min)	3.3 (0.8)	3.8 (0.8)	3.9 (0.8)	4.1 (0.9)	4.7 (0.8)	< 0.001
Respiratory quotient	0.85 (0.06)	0.82 (0.56)	0.82 (0.05)	0.81 (0.07)	0.82 (0.09)	0.305

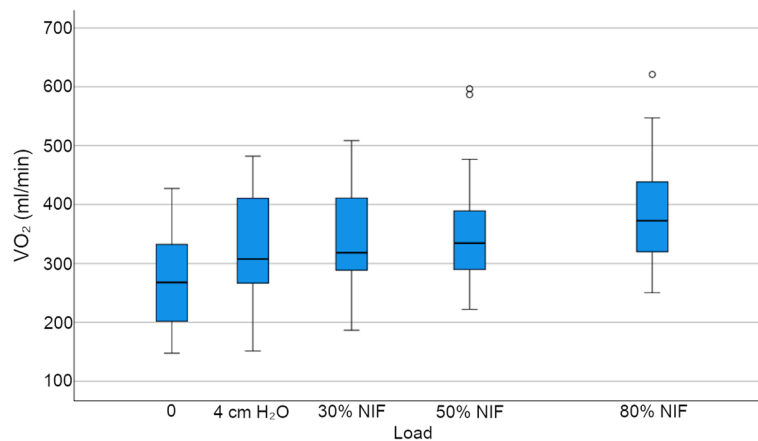Data presented as mean (SD)

Fig. 4 First session VO$_2$. Box and whisker plot detailing first session VO$_2$ (ml/min) at 0 (baseline), 4 cmH$_2$O and at 30, 50 and 80% NIF load

First session baseline mean (SD) VO_2 was 276 (86) ml/min, and differed significantly with IMT load (Table 2 and Fig. 4). Two participants did not perform 50% NIF IMT (declined), and seven participants did not complete 80% NIF ($n = 4$ declined, $n = 3$ IMT device used did not reach the participant's 80% NIF resistance). Post hoc comparisons revealed significant differences in VO_2 between baseline and 50% NIF and baseline and 80% NIF ($p = 0.048$ and $p = 0.001$, respectively).

First session baseline VO_2 ml/kg/min did not correlate with NIF, Sepsis Organ Failure Score (SOFA), P/F ratio, pressure support (PS), positive end expiratory pressure (PEEP), P0.1, vasopressor inotrope score (VIS) or C-reactive protein (CRP).

Mean (SD) percentage increase in oxygen consumption compared to baseline was 19.7 (22.2) %, 23.6 (24.8) %, 31.2 (25.0) % and 44.0 (33.6) % after IMT at 4 cmH_2O and 30, 50 and 80% NIF, respectively.

There were no significant differences in respiratory quotient between baseline and all IMT doses (Table 2).

Effect of baseline physiological factors on VO_2

Linear mixed effects models showed a dose–response slope of 9.3 ml/min/cmH_2O (95% confidence intervals 5.1–13.4 $p < 0.001$); indicating VO_2 increases by 9.3 ml/min for every 1 cmH_2O increase in inspiratory load from IMT. Every increase in P/F ratio of 1 decreases the intercept by 0.41 (CI − 0.58 to − 0.24 $p < 0.001$), demonstrating better oxygenated patients have a lower baseline VO_2. P/F ratio did not affect the dose–response slope.

Baseline NIF had a significant effect on the intercept and slope, with every 1cmH_2O increase in NIF increasing intercept VO_2 by 3.28 ml/min (CI 1.98–4.59 $p < 0.001$) and decreasing the dose–response slope by − 0.15 ml/min/cmH_2O (CI − 0.24 to − 0.05 $p = 0.002$). This indicates that patients with a higher NIF have a higher resting VO_2, but a less pronounced increase in VO_2 as the inspiratory load increases.

SOFA, CRP, P0.1, shunt and session number had no significant influence on intercept or slope.

Effect of IMT on pulmonary shunt

Our data found no significant change in percentage of pulmonary shunt after IMT; mean (SD) percentage pulmonary shunt was 14.5 (6.9) at baseline and 14.7 (6.7) after IMT ($p = 0.873$).

Discussion

We present novel data documenting the metabolic cost of IMT in mechanically ventilated patients in critical care. We show that IMT causes a statistically significant and load-dependent increase in VO_2 in patients during the recovery phase of critical illness. P/F ratio and NIF impact the baseline VO_2. The dose–response relationship of the applied respiratory load during IMT is modulated by respiratory strength.

Significance of the findings

The load-dependent increase in VO_2 during IMT in mechanically ventilated patients shown in our data is in agreement with data in healthy participants performing both

peripheral muscle resistance loading [21, 24] and progressive inspiratory threshold loading [25] where a higher mechanical load leads to increased oxygen consumption.

Progressive resistive inspiratory loading and its associated increase in VO_2 will inevitably result in task failure with sufficient load and/duration [24]; therefore, it is of great importance to stratify which patients in ICU can tolerate higher respiratory loading during IMT. Some current data suggest patients with a maximal inspiratory pressure of ≥ 28 cmH_2O and a moderate to high quality of life are most likely to derive a respiratory muscle strength benefit when IMT was performed after liberation from the ventilator [26]. Our data offer further insight into which patients could benefit most from IMT.

Physiologically, these data show that better oxygenated patients, as measured by P/F ratio, have lower VO_2 at rest and with IMT. Reduced respiratory effort to maintain adequate oxygenation could explain this relationship and indicates better oxygenated patients (as measured by P/F ratio) may have a greater metabolic reserve to tolerate IMT.

It is interesting that a higher NIF increases oxygen consumption in this cohort of patients. Healthy data show that participants with a higher peripheral muscle bulk have a greater resting VO_2 than weight matched controls [27]. Given that diaphragm thickness and quadriceps thickness correlate in mechanically ventilated patients [28], higher diaphragm muscle bulk could explain a higher resting VO_2 in this population studied. Maximal inspiratory pressure and diaphragm thickness are correlated in healthy participants [29, 30]; although there are no data unequivocally demonstrating a correlation between thickness and strength in mechanically ventilated patients [31], we would expect these parameters to be related.

The relationship between NIF and VO_2 response at higher resistive loads is an important finding in this study; Increased strength or endurance of respiratory muscles can reduce their metabolic demand [32]. In patients with heart failure, NIF strongly correlates with maximum oxygen consumption [33], explaining the relationship that patients with stronger inspiratory muscles are able to tolerate higher training loads. Muscle contraction during exercise, and ultimately muscle strengthening requires adenosine triphosphate (ATP) and an increase in VO_2 [34]. There is conflicting evidence on the role of VO_2 and its relationship to weaning or task failure in mechanically ventilated patients; some studies have found that an increased VO_2 during the weaning phase is associated with weaning failure [35–37]. Conversely, one study found the opposite; patients who have proportionally greater increases in VO_2 when exposed to less ventilatory support are more likely to sustain a weaning trial [38]. Task failure is dependent on the amount of energy expended during breathing [39]; our data show that patients with a higher NIF have a less pronounced increase in VO_2 with progressive IMT loads, indicating this cohort of patients could tolerate higher IMT loads than patients with a lower NIF.

Persistent catabolism and hypermetabolism to meet the high energy requirements of critical illness leads to depletion of lean body mass and altered mitochondrial function [34]. This is likely to result in decreased ATP production, meaning critically ill patients may not be able to perform effective muscle contraction and force generation, indicated by an increase in VO_2 [16]. Our study focussed on those during the recovery phase, and whilst there was a significant change in VO_2 with IMT, markers of inflammation (CRP) and sepsis (SOFA) had no impact on VO_2 at rest or with respiratory loading. This is in

agreement with other data that found CRP is not associated with overall energy expenditure in critically ill patients [40].

One reported concern of IMT is that disconnection from the ventilator circuit and the applied respiratory load may cause de-recruitment and atelectasis [10]. Hence, we measured shunt before and after IMT and found no significant change in shunt pre- and post-IMT. Although IMT in this study was performed in-line with the ventilator, pressure support was set to 0 cmH_2O, and the insertion and removal of the IMT device and flow sensor required breaking the ventilator circuit five times; similar to IMT in normal practice. Whilst this is the first study to our knowledge to measure changes in shunt peri-IMT procedure, the level of de-recruitment after IMT may depend on respiratory rate and tidal volume during IMT, as observed in spontaneous breathing trials [41]; parameters which were not measured in this study. This limitation and the relatively small number of measurements made in this study ($n=41$) means this finding requires further validation.

Critique of the method

This study has some limitations. It is important to acknowledge that the population of patients studied were recruited from specialist medical, surgical and transplant ICUs, meaning it is not possible to extrapolate these findings to all mechanically ventilated patients in ICU. It was unusual we saw a predominance of male participants in this convenience sample. Tolerance of increasing inspiratory load in ventilator-dependent patients is complex and has both physiological and psychological elements [36–39], meaning not all patients will tolerate the increased inspiratory load imposed by IMT. In our study, 2 participants declined further IMT after 4 cmH_2O load due to increased work of breathing during IMT, and the study procedure was ceased in one participant due to an increase in their respiratory rate to > 35 breaths per minute after connection of the IMT device. Intolerance of IMT shown in this study and the small number of eligible screened patients (owing to neurological compromise, sedation and ECMO) highlights the challenging reality of performing IMT in critically ill, mechanically ventilated patients.

Whilst the indirect calorimetry used in this study was feasible it required extensive analysis to gain meaningful data. It would be difficult to measure VO_2 during IMT in 'real time' during a clinical session to aid prescription; this highlights the importance of the physiological markers discussed that could aid prescription of IMT in mechanically ventilated patients. Breathing parameters during IMT such as inspiratory flow rate, respiratory rate, tidal volume, respiratory duty cycle and work of breathing were not recorded in this study. These variables will impact work of breathing and muscle power generated by the inspiratory muscles, and in turn have the potential to affect oxygen consumption during loaded breathing with IMT [15]. This is important to note when interpreting our results, and future studies investigating the metabolic cost of IMT should explore the impact of these factors on oxygen consumption during IMT.

The Philips Respironics® Threshold IMT and PEP devices were specifically used in this study as they allowed a contiguous ventilator circuit for accurate VO_2 analysis. As the device has a maximum threshold resistance of 41 cmH_2O, we were unable to measure the response to IMT at 80% NIF in participants with a NIF > 51.2 cmH_2O. Future studies

of this nature should incorporate a device capable of a higher maximum threshold load, to measure VO_2 response in patients with a higher respiratory strength; although we are aware this may require IMT device development.

As an exploratory study, we did not perform a power analysis. Statistical analysis of repeated sessions in the same participant with the same NIF was not possible, owing to the fact NIF was only assessed every 5–7 days but IMT was performed up to 4 days per week. Subjective tolerability of IMT at each training level was not assessed as participants only performed two sets at each level rather than five sets as commonly cited in the literature. Long-term outcomes such as respiratory strength, QOL and breathlessness were not assessed, owing to the observational nature of this study. Whilst an optimal IMT technique was encouraged during the study, objective measurements of inspiratory muscle physiology such as electromyography or near-infrared spectroscopy (NIRS) was not used. For example, patients with a lower NIF could have increased accessory muscle use during IMT at higher loads, affecting their oxygen consumption, NIRS could also offer greater insight into oxygenation at the muscle level, giving further insight into muscle recruitment during different loads of IMT.

Conclusions

This study has given the first insight into the physiological demands of IMT in critically ill patients. Our data show the metabolic cost of IMT in mechanically ventilated patients, but importantly, which patients may be able to better tolerate IMT during recovery from critical illness. This approach may help develop a more individualised approach to clinicians' prescription of IMT in mechanically ventilated patients, rather than a universal percentage NIF as commonly cited. Our results will advise future studies in larger more diverse populations which may include measurement of muscle activity and tolerability.

Abbreviations

MV	Mechanical ventilation
IMT	Inspiratory muscle training
ICU	Intensive care unit
VO_2	Oxygen consumption
FiO_2	Fraction of inspired oxygen
ECMO	Extracorporeal membrane oxygenation
VCO_2	Carbon dioxide production
PEP	Positive expiratory pressure
NIF	Negative inspiratory force
LLM	Linear mixed model
SOFA	Sepsis Organ Failure Score
PS	Pressure support
PEEP	Positive end expiratory pressure
VIS	Vasopressor inotrope score
CRP	C-reactive protein
ATP	Adenosine tri-phosphate
NIRS	Near-infrared spectroscopy

Supplementary Information

Additional file 1. Appendix A: Reasons for discontinuation of study data collection. **Appendix B**: Measurement of negative inspiratory force (NIF). **Appendix C**: Detailed patient diagnosis.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the local research and development department, the Wales research ethics committee 4 (Reference 21/WA/0268) on 14th September 2021, and the Health Research Authority on 15th September 2021. The study is registered on ClinicalTrials.gov, registration number: NCT05101850**.** The study was conducted according to the Declaration of Helsinki as most recently amended and Good Clinical Practice standards. Patients who had capacity gave informed consent to participate in the study. Advice was sought from a personal consultee to give approval to participate in the study if patients did not have capacity to give informed consent. This process was approved by the ethics committee.

Consent for publication
Not applicable.

Competing interests
The institution to which of MKP, SER, DSK are affiliated has received funding from Mermaid Care A/S. DSK and SER have performed consultancy work for Mermaid Care A/S who manufacture the Beacon Caresystem. SER is a board member and a minor shareholder in Mermaid Care A/S. MIP is a paid consultant for Philips Respironics; however, Philips had no role in this study.

References
1. Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, Zhu J, Sachdeva R, Sonnad S, Kaiser LR, Rubinstein NA, Powers SK, Shrager JB (2008) Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 358(13):1327–1335. https://doi.org/10.1056/NEJMoa070447
2. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, Vorona S, Sklar MC, Rittayamai N, Lanys A, Murray A, Brace D, Urrea C, Reid WD, Tomlinson G, Slutsky AS, Kavanagh BP, Brochard LJ, Ferguson ND (2018) Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. Am J Respir Crit Care Med 197(2):204–213. https://doi.org/10.1164/rccm.201703-0536OC
3. Dres M, Dubé BP, Mayaux J, Delemazure J, Reuter D, Brochard L, Similowski T, Demoule A (2017) Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. Am J Respir Crit Care Med 195(1):57–66. https://doi.org/10.1164/rccm.201602-0367OC
4. Jung B, Moury PH, Mahul M, de Jong A, Galia F, Prades A, Albaladejo P, Chanques G, Molinari N, Jaber S (2016) Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. Intensive Care Med 42(5):853–861. https://doi.org/10.1007/s00134-015-4125-2
5. Bissett B, Leditschke IA, Neeman T, Boots R, Paratz J (2015) Weaned but weary: one third of adult intensive care patients mechanically ventilated for 7 days or more have impaired inspiratory muscle endurance after successful weaning. Heart Lung 44(1):15–20. https://doi.org/10.1016/j.hrtlng.2014.10.001
6. De Jonghe B, Bastuji-Garin S, Durand MC, Malissin I, Rodrigues P, Cerf C, Outin H, Sharshar T, Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation (2007) Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. Crit Care Med 35(9):2007–2015. https://doi.org/10.1097/01.ccm.0000281450.01881.d8
7. Supinski GS, Westgate P, Callahan LA (2016) Correlation of maximal inspiratory pressure to transdiaphragmatic twitch pressure in intensive care unit patients. Crit Care (London, England) 20:77. https://doi.org/10.1186/s13054-016-1247-z
8. Damuth E, Mitchell JA, Bartock JL, Roberts BW, Trzeciak S (2015) Long-term survival of critically ill patients treated with prolonged mechanical ventilation: a systematic review and meta-analysis. Lancet Respir Med 3(7):544–553. https://doi.org/10.1016/S2213-2600(15)00150-2
9. Sklar MC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, Rittayamai N, Harhay MO, Reid WD, Tomlinson G, Rozenberg D, McClelland W, Riegler S, Slutsky AS, Brochard L, Ferguson ND, Goligher EC (2020) Association of low

baseline diaphragm muscle mass with prolonged mechanical ventilation and mortality among critically ill adults. JAMA Netw Open 3(2):e1921520. https://doi.org/10.1001/jamanetworkopen.2019.21520

10. Hearn E, Gosselink R, Freene N, Boden I, Green M, Bissett B (2022) Inspiratory muscle training in intensive care unit patients: an international cross-sectional survey of physiotherapist practice. Aust Crit Care 35(5):527–534. https://doi.org/10.1016/j.aucc.2021.08.002

11. Bissett B, Leditschke IA, Green M, Marzano V, Collins S, Van Haren F (2019) Inspiratory muscle training for intensive care patients: a multidisciplinary practical guide for clinicians. Aust Crit Care 32(3):249–255. https://doi.org/10.1016/j.aucc.2018.06.001

12. Vorona S, Sabatini U, Al-Maqbali S, Bertoni M, Dres M, Bissett B, Van Haren F, Martin AD, Urrea C, Brace D, Parotto M, Herridge MS, Adhikari NKJ, Fan E, Melo LT, Reid WD, Brochard LJ, Ferguson ND, Goligher EC (2018) Inspiratory muscle rehabilitation in critically ill. Adults a systematic review and meta-analysis. Ann Am Thoracic Soc 15(6):735–744. https://doi.org/10.1513/AnnalsATS.201712-961OC

13. Elkins M, Dentice R (2015) Inspiratory muscle training facilitates weaning from mechanical ventilation among patients in the intensive care unit: a systematic review. J Physiother 61(3):125–134. https://doi.org/10.1016/j.jphys.2015.05.016

14. Martin AD, Smith BK, Davenport PD, Harman E, Gonzalez-Rothi RJ, Baz M, Layon AJ, Banner MJ, Caruso LJ, Deoghare H, Huang TT, Gabrielli A (2011) Inspiratory muscle strength training improves weaning outcome in failure to wean patients: a randomized trial. Crit Care (London, England) 15(2):R84. https://doi.org/10.1186/cc10081

15. McCool FD, Tzelepis GE, Leith DE, Hoppin FG Jr (1989) Oxygen cost of breathing during fatiguing inspiratory resistive loads. J Appl Physiol (Bethesda, Md. 1985) 66(5):2045–2055. https://doi.org/10.1152/jappl.1989.66.5.2045

16. Bear DE, Parry SM, Puthucheary ZA (2018) Can the critically ill patient generate sufficient energy to facilitate exercise in the ICU? Curr Opin Clin Nutr Metab Care 21(2):110–115. https://doi.org/10.1097/MCO.0000000000000446

17. Black C, Grocott M, Singer M (2020) The oxygen cost of rehabilitation interventions in mechanically ventilated patients: an observational study. Physiotherapy 107:169–175. https://doi.org/10.1016/j.physio.2019.06.008

18. Collings N, Cusack R (2015) A repeated measures, randomised cross-over trial, comparing the acute exercise response between passive and active sitting in critically ill patients. BMC Anesthesiol 15(1):1. https://doi.org/10.1186/1471-2253-15-1

19. Sommers J, Klooster E, Zoethout SB, van den Oever HLA, Nollet F, Tepaske R, Horn J, Engelbert RHH, van der Schaaf M (2019) Feasibility of exercise testing in patients who are critically ill: a prospective, observational multicenter study. Arch Phys Med Rehabil 100(2):239–246. https://doi.org/10.1016/j.apmr.2018.07.430

20. Poulsen MK, Thomsen LP, Kjaergaard S, Rees SE, Karbing DS (2019) Reliability of, and agreement between, two breath-by-breath indirect calorimeters at varying levels of inspiratory oxygen. Nutr Clin Pract 34(5):767–774. https://doi.org/10.1002/ncp.10250

21. Slingerland-Boot H, Adhikari S, Mensink MR, van Zanten ARH (2022) Comparison of the Beacon and Quark indirect calorimetry devices to measure resting energy expenditure in ventilated ICU patients. Clin Nutr ESPEN 48:370–377. https://doi.org/10.1016/j.clnesp.2022.01.015

22. Buitrago S, Wirtz N, Flenker U, Kleinöder H (2014) Physiological and metabolic responses as function of the mechanical load in resistance exercise. Appl Physiol Nutr Metab Physiologie appliquee, Nutrition et Metabolisme 39(3):345–350. https://doi.org/10.1139/apnm-2013-0214

23. Thomsen LP, Karbing DS, Smith BW, Murley D, Weinreich UM, Kjærgaard S, Toft E, Thorgaard P, Andreassen S, Rees SE (2013) Clinical refinement of the automatic lung parameter estimator (ALPE). J Clin Monit Comput 27(3):341–350. https://doi.org/10.1007/s10877-013-9442-9

24. Phelain JF, Reinke E, Harris MA, Melby CL (1997) Postexercise energy expenditure and substrate oxidation in young women resulting from exercise bouts of different intensity. J Am Coll Nutr 16(2):140–146. https://doi.org/10.1080/07315724.1997.10718664

25. Eastwood PR, Hillman DR, Morton AR, Finucane KE (1998) The effects of learning on the ventilatory responses to inspiratory threshold loading. Am J Respir Crit Care Med 158(4):1190–1196. https://doi.org/10.1164/ajrccm.158.4.9803108

26. Bissett BM, Wang J, Neeman T, Leditschke IA, Boots R, Paratz J (2020) Which ICU patients benefit most from inspiratory muscle training? Retrospective analysis of a randomized trial. Physiother Theory Pract 36(12):1316–1321. https://doi.org/10.1080/09593985.2019.1571144

27. McInnis KJ, Balady GJ (1999) Effect of body composition on oxygen uptake during treadmill exercise: body builders versus weight-matched men. Res Q Exerc Sport 70(2):150–156. https://doi.org/10.1080/02701367.1999.10608032

28. Supinski GS, Netzel PF, Westgate PM, Schroder EA, Wang L, Callahan LA (2022) Magnetic twitch assessment of diaphragm and quadriceps weakness in critically ill mechanically ventilated patients. Respir Physiol Neurobiol 295:103789. https://doi.org/10.1016/j.resp.2021.103789

29. Cardenas LZ, Santana PV, Caruso P, Ribeiro de Carvalho CR, Pereira de Albuquerque AL (2018) Diaphragmatic ultrasound correlates with inspiratory muscle strength and pulmonary function in healthy subjects. Ultrasound Med Biol 44(4):786–793. https://doi.org/10.1016/j.ultrasmedbio.2017.11.020

30. Holtzhausen S, Unger M, Lupton-Smith A, Hanekom S (2018) An investigation into the use of ultrasound as a surrogate measure of diaphragm function. Heart Lung J Crit Care 47(4):418–424. https://doi.org/10.1016/j.hrtlng.2018.04.010

31. Dubé BP, Dres M, Mayaux J, Demiri S, Similowski T, Demoule A (2017) Ultrasound evaluation of diaphragm function in mechanically ventilated patients: comparison to phrenic stimulation and prognostic implications. Thorax 72(9):811–818. https://doi.org/10.1136/thoraxjnl-2016-209459

32. Romer LM, Polkey MI (2008) Exercise-induced respiratory muscle fatigue: implications for performance. J Appl Physiol (Bethesda, Md. 1985) 104(3):879–888. https://doi.org/10.1152/japplphysiol.01157.2007

33. Chua TP, Anker SD, Harrington D, Coats AJ (1995) Inspiratory muscle strength is a determinant of maximum oxygen consumption in chronic heart failure. Br Heart J 74(4):381–385. https://doi.org/10.1136/hrt.74.4.381

34. Moonen HPFX, Beckers KJH, van Zanten ARH (2021) Energy expenditure and indirect calorimetry in critical illness and convalescence: current evidence and practical considerations. J Intensive Care 9(1):8. https://doi.org/10.1186/s40560-021-00524-0

35. Shikora SA, Bistrian BR, Borlase BC, Blackburn GL, Stone MD, Benotti PN (1990) Work of breathing: reliable predictor of weaning and extubation. Crit Care Med 18(2):157–162

36. Miwa K, Mitsuoka M, Takamori S, Hayashi A, Shirouzu K (2003) Continuous monitoring of oxygen consumption in patients undergoing weaning from mechanical ventilation. Respir Int Rev Thoracic Dis 70(6):623–630. https://doi.org/10.1159/000075209

37. Mitsuoka M, Kinninger KH, Johnson FW, Burns DM (2001) Utility of measurements of oxygen cost of breathing in predicting success or failure in trials of reduced mechanical ventilatory support. Respir Care 46(9):902–910

38. Bellani G, Foti G, Spagnolli E, Milan M, Zanella A, Greco M, Patroniti N, Pesenti A (2010) Increase of oxygen consumption during a progressive decrease of ventilatory support is lower in patients failing the trial in comparison with those who succeed. Anesthesiology 113(2):378–385. https://doi.org/10.1097/ALN.0b013e3181e81050

39. Roussos C, Macklem PT (1982) The respiratory muscles. N Engl J Med 307(13):786–797

40. Mtaweh H, Soto Aguero MJ, Campbell M, Allard JP, Pencharz P, Pullenayegum E, Parshuram CS (2019) Systematic review of factors associated with energy expenditure in the critically ill. Clin Nutr ESPEN 33:111–124. https://doi.org/10.1016/j.clnesp.2019.06.009

41. Longhini F, Maugeri J, Andreoni C, Ronco C, Bruni A, Garofalo E, Pelaia C, Cavicchi C, Pintaudi S, Navalesi P (2019) Electrical impedance tomography during spontaneous breathing trials and after extubation in critically ill patients at high risk for extubation failure: a multicenter observational study. Ann Intensive Care 9(1):88. https://doi.org/10.1186/s13613-019-0565-0

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