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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

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ABSTRACT

Objectives: The purpose of this study was to establish whether intensive care unit (ICU) patients have impaired inspiratory muscle (IM) endurance immediately following weaning from prolonged mechanical ventilation (MV), and whether IM weakness is related to function or perceived exertion.

Background: Impaired IM endurance may hinder recovery from MV, however it is unknown whether this affects patients' function or perceived exertion.

Methods: Prospective observational study of 43 adult ICU patients following weaning from MV (>7 days duration). IM endurance was measured using the fatigue resistance index (FRI).

Results: IM endurance was impaired (FRI = mean 0.90, SD 0.31), with 37% scoring below 0.80. IM strength did not significantly correlate with function ($r = 0.24$, $p = 0.12$) or perceived exertion during exercise ($r = -0.146$, $p = 0.37$).

Conclusions: IM endurance is reduced in one third of patients, while IM weakness does not appear closely associated with function or perceived exertion immediately following successful weaning.

Introduction

Intensive care unit (ICU) patients frequently experience peripheral muscle wasting and these changes are detectable very early in the admission. Early rapid proteolysis occurs in the diaphragm muscles of ventilated patients.[1] Inspiratory muscle weakness, manifesting as a reduction in maximum inspiratory pressure (MIP), is also associated with limb muscle weakness in ICU patients.[2] Thus proteolysis of both the skeletal muscles and diaphragm are likely to complicate illness and affect the recovery trajectory for many ICU patients.

The resulting diaphragmatic weakness is a potential contributor to difficulty in weaning from mechanical ventilation.[3] However, few studies to date have measured functional endurance of the diaphragm in this patient group. This is surprising, as diaphragmatic endurance, rather than force, is required to achieve breathing independently of the mechanical ventilator.

In 2005 Chang and colleagues[4] demonstrated that respiratory muscle endurance is impaired for some time after successful

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weaning from mechanical ventilation. In addition, impaired endurance is negatively associated with duration of mechanical ventilation ($r = -0.65$, $p = 0.007$).

To our knowledge, the relationship between respiratory muscle weakness (impaired strength or endurance) and global functional measures in ICU patients (e.g., Barthel Index, Acute Care Index of Function) has not been explored. Functional status (i.e. the ability to transfer and mobilize independently) is important for longer term outcomes and quality of life. It is plausible that difficulty breathing, secondary to residual respiratory muscle weakness, may impact on the functional status of ICU survivors. It is therefore important to establish the relationship between respiratory muscle weakness and physical function in ICU patients.

Perceived exertion may also impact on functional status, but remains uninvestigated. In the context of mobilizing intensive care patients, patient dyspnea or perceived exertion during exercise is likely related to inspiratory muscle weakness. In athletes, perception of dyspnea may be the limiting factor during high-intensity endurance exercise.[5] Whether this contributes to functional limitation in mobilizing intensive care patients warrants investigation.

Thus the aim of this study was to answer the following questions:

1. In adult intensive care patients who have been recently weaned from 7 days or more of mechanical ventilation, is inspiratory muscle endurance impaired?
2. Is there a relationship between inspiratory muscle weakness, functional status and perceived exertion following successful ventilator weaning in this group?

Methods

Design

This prospective observational study is a sub-study of a larger trial[6] of outcomes in ICU patients ventilated for 7 days or longer. The present study analyses the baseline data collected for 43 subjects eligible for inclusion in the post-weaning study between February 2011 and December 2013. The study was approved by the Australian Capital Territory Health Human Research Ethics Committee and patients provided their own written informed consent.

Setting

This prospective study occurred in a single tertiary 22 bed mixed medical/surgical ICU in Canberra, Australia. This unit practices minimal sedation and early rehabilitation as the standard of care, whereby both nursing and physiotherapy staff facilitate sitting out of bed and mobilization of patients as early as possible (in the absence of established contraindications).[7]

Participants

All patients ventilated for 7 days or longer were screened for inclusion in this study once successfully extubated for 48 h. Patients were included if they were able to provide informed consent, were alert (Riker Sedation and Agitation Scale = 4)[8] and able to participate actively in inspiratory muscle training, and rate their dyspnea via a modified Borg scale.[9] Patients were excluded if they were <16 years of age, pregnant, had heart rates, respiratory rates, blood pressure or oxygen saturation outside stated limits, had active infection[6] or were likely to be palliated imminently. Patients were also excluded from the study if they had participated in specific inspiratory muscle strengthening while ventilated. Fig. 1 illustrates the flow of patients through the study. The most frequent reason for exclusion was impaired neurological status with an inability to follow commands ($n = 62$).

Variables and measures

The primary measure was inspiratory muscle endurance, measured as the Fatigue Resistance Index (FRI). Using the same protocol described previously by Chang and colleagues,[4] this test compares Maximum Inspiratory Pressures (MIP) before and after a 2 minute loading challenge, where patients breathe through a resistance of 30% of MIP. MIP is measured from residual volume using a handheld device (MicroRPM Respiratory Pressure Meter), in accordance with the protocol recommended by the American Thoracic Society and European Respiratory Society.[10] This requires patients to inhale maximally from residual volume, sustaining the effort for at least 1 second. Efforts are repeated three times to ensure less than 20% variability between measurements. This method of measuring MIP is both reliable and valid using portable handheld devices.[11] FRI is calculated as the post–challenge MIP divided by the pre-challenge MIP (scores <1.00 indicate the presence of fatigue).

The secondary measures include patients' rate of perceived exertion (RPE) using a modified Borg scale (0–10)[9] which has acceptable reliability and validity in ICU patients.[12] Patients self-reported their RPE both at rest and during peak exercise. As peak exercise varied between patients (e.g., from sitting on the edge of the bed, to mobilizing around the ICU) depending on ability, patients were asked to report the highest exertion they experienced during any form of exercise on the day of measurement. All MIP, FRI and RPE measures were completed by specifically trained research staff.

Global function was measured by the treating physiotherapist using the Acute Care Index of Function (ACIF) tool[13] which has good inter-rater reliability[14] and construct validity[15] in acute neurological patients.

Data analysis

Based on a previous study,[4] we estimated that a sample size of 16 patients would be required to detect a change in 10% of MIP when measuring FRI (correlation co-efficient of >0.6). Normalized values for MIP scores were calculated using the method outlined by Evans and colleagues.[16] Parametric correlations were performed between variables, with statistical significance considered

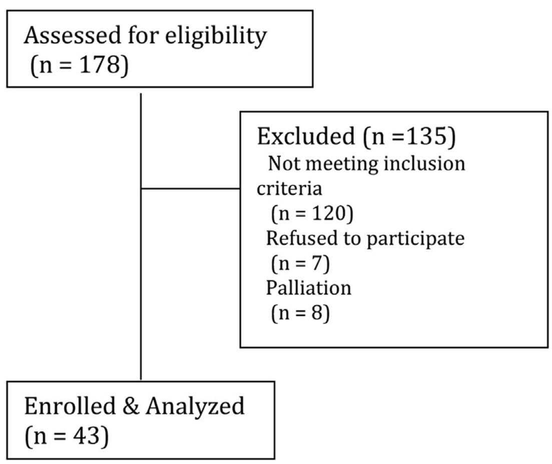

Fig. 1. Flow of participants through study.

as $p < 0.05$. Due to the skewed nature of the RPE data, non-parametric correlations were also calculated (Spearman's Rho) but results were consistent with parametric calculations and thus are not reported. All statistical analyses were performed using SPSS version 22.

Results

Participants

The characteristics of the 43 patients (30 male, 13 female) included in the study are summarized in Table 1. The most common diagnosis in this cohort was pneumonia ($n = 9$) followed by sepsis ($n = 7$) and multitrauma ($n = 6$).

The mean duration of ventilation was 10.8 days (range 7–26 days) (see Table 2), with most patients ventilated in spontaneous (pressure support) modes for the majority of their ventilation period (mean 8.9 days, range 1–24 days). The other 2 modes of ventilation used were synchronized intermittent mandatory ventilation (SIMV) and pressure control ventilation plus (PCV+). Sedation was used in all patients (predominantly propofol), with a mean sedation-free period of 4.8 days. There was wide variability in functional level (ACIF scores), ranging from 8 to 92 (mean 40.3).

While the mean FRI was below 1.0 (0.90, SD 0.319), there was considerable spread in the sample (see Fig. 2), such that 15 (37%) of patients scored less than 0.80, while 4 (10%) scored above 1.20, including one notable outlier at 2.0.

There was also wide variability in MIP scores (see Fig. 3), with one patient scoring 86% of their predicted MIP (87). This patient had an FRI of 1.06, i.e. no evidence of fatigability. In contrast, the patient with the lowest MIP score (6) had an FRI of 0.33, indicating severely impaired fatigue resistance. MIP was significantly positively correlated with FRI ($r = 0.39$, $p = 0.01$) (see Fig. 4a).

There was a weak positive trend (see Fig. 4b), but no significant correlation between MIP scores and functional (ACIF) scores ($r = 0.243$, $p = 0.121$).

Of the 43 patients, 17 (40%) reported an RPE greater than zero at rest. While RPE at rest was strongly correlated with RPE during

Table 1
Characteristics of participants.

Age	Sex	Diagnosis	APACHE II scores	Duration of ventilation (days)	Spontaneous ventilation (PSV[a] only) days	SIMV[b]/PCV + [c] days	Sedation[d]	Sedation free days[e]	ACIF[f]
57	Male	Multitrauma	13	8	5	3	P, O, B	3	8
39	Male	Chest multitrauma	6	7	3	4	P	3	8
45	Male	Community acquired pneumonia	10	8	7	1	P, O, B	1	70
68	Male	Chest & pelvic trauma	18	7	6	1	P	0	17
52	Male	Multitrauma	22	11	6	5	O,B	6	17
81	Male	Hepatectomy	19	12	12	0	P, B	7	38
64	Male	Chest trauma	33	19	15	4	P, O, B	6	20
64	Female	Acute hepatic failure	40	7	3	4	P	4	60
69	Female	Middle cerebral artery CVA	27	10	10	0	P	2	60
43	Female	Sepsis	18	11	10	1	P, O	2	40
81	Female	Sepsis, pneumonia	17	8	7	1	P	7	37
81	Male	AAA repair	14	9	6	3	P, O, B	7	34
66	Male	Chest multitrauma	20	11	10	1	P	9	47
60	Male	Septic shock	25	16	15	1	P, B	0	50
70	Male	Bacterial pneumonia	23	9	8	1	P, B, D	1	31
77	Female	Respiratory arrest	17	9	8	1	P	6	29
49	Female	Necrotizing fasciitis	21	9	7	2	P, B	0	16
55	Female	Status epilepticus	15	13	5	8	P, B	7	26
47	Male	Hospital acquired pneumonia	25	9	8	1	P	8	49
67	Male	Bacterial pneumonia	16	22	21	1	P	17	50
43	Male	Hepatorenal syndrome	25	16	14	2	P, O	11	57
66	Female	Acute pulmonary edema	16	9	8	1	P	7	20
49	Male	Left lung hematoma	17	16	13	3	P, B, D	2	20
85	Male	Hyponatraemia	33	8	7	1	P, B	5	92
63	Female	Bilateral pneumonia	29	9	9	0	P	5	40
63	Male	Bacterial meningitis	25	8	6	2	P, O, B, D	0	30
77	Male	Perforated duodenal ulcer	24	26	24	2	P	17	25
79	Male	Community acquired pneumonia	15	7	7	0	P	4	70
76	Male	Sepsis, pneumonia	12	8	8	0	P	6	40
61	Male	Vasculitis	10	7	7	0	P	6	70
85	Male	CABG	23	8	7	1	P	5	42
66	Male	Sepsis, multiple organ dysfunction	28	11	11	0	P	6	15
72	Male	Multifactorial respiratory failure	15	13	13	0	P	4	50
42	Female	Sepsis unclear origin	28	11	11	0	P, O	1	15
48	Male	Multiple organ failure	21	12	12	0	P	0	16
62	Male	Post CABG pleural effusions	24	10	7	3	P	7	56
80	Female	CABG	39	13	11	2	P	10	17
86	Male	Cardiogenic shock	31	13	10	3	P, B, D	0	58
41	Female	Exacerbation of asthma	21	9	5	4	P, O, B, D	0	17
43	Female	Staph aureus bacteremia	14	7	2	5	P	3	63
55	Male	Community acquired pneumonia	24	7	1	4	P	5	60
24	Male	Neutropenic respiratory sepsis	16	10	7	3	P, O, B, D	2	64
48	Male	MVA chest trauma	20	10	9	1	P, O, B	5	87

[a] PSV = pressure support ventilation.
[b] SIMV = synchronized intermittent mandatory ventilation.
[c] PCV+ = pressure control ventilation plus.
[d] Sedation: where P = propofol, O = opioid (e.g. Morphine), B = benzodiazepines, D = dexmedetomidine (recorded as any dose delivered on any day).
[e] Sedation free days – full days where no sedation of any kind was administered during the ventilation period.
[f] ACIF = Acute Care Index of Function (score/100).

Table 2
Characteristics of participants and summary of measures.

	Mean	Standard Deviation	Range
Age (years)	61.6	15.17	24–86
Apache II score (admission)	21.1	7.45	6–40
Total duration of ventilation (days)	10.8	4.11	7–26
Pressure support ventilation (days)	8.9	4.48	1–24
Sedation-free period (days)	4.8	4.01	0–17
Acute Care Index of Function (score/100)	40.3	21.7	8–92
Maximum inspiratory pressure (cm H_2O)	34.2	19.4	6–87
Maximum inspiratory pressure (% predicted)	38.6	19.7	6–86
Fatigue resistance index (FRI)	0.90	0.32	0.21–2.00
Rate of perceived exertion (rest) (score/10)	1.95	2.78	0–9
Rate of perceived exertion (exercise) (score/10)	3.40	3.50	0–10

exercise ($r = 0.78$, $p < 0.01$) (see Fig. 4c), there were no significant correlations between RPE and ACIF, MIP or FRI (see Table 3). Duration of ventilation and APACHE II scores were not correlated with ACIF, MIP or FRI (see Table 3).

Discussion

The results of this study provide further evidence that inspiratory muscle endurance is often impaired in ICU patients who have been recently weaned from mechanical ventilation of at least 7 days duration, even if the patients have been ventilated predominantly with spontaneous modes (e.g. pressure support). However there does not appear to be a close relationship between inspiratory muscle weakness and either function or perceived exertion in this cohort.

Our findings regarding impaired fatigue resistance (FRI 0.90) within 48 h of weaning from mechanical ventilation are consistent with previous findings.[4] Chang and colleagues demonstrated a mean FRI of 0.88 in a group of 20 subjects who had been ventilated for a mean of 4.6 days and were followed up on average 7 days (range 2–16) following weaning. The consistency in the magnitude of the observed FRI deficit suggests that impairments in FRI may be mostly attributable to changes that occur within the first few days

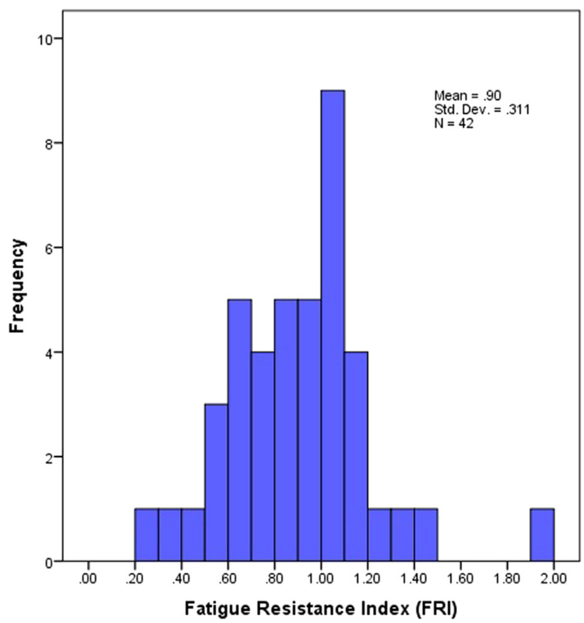

Fig. 2. Frequency distribution of Fatigue Resistance Index, where scores below 1.0 indicate a drop in strength after an endurance challenge.

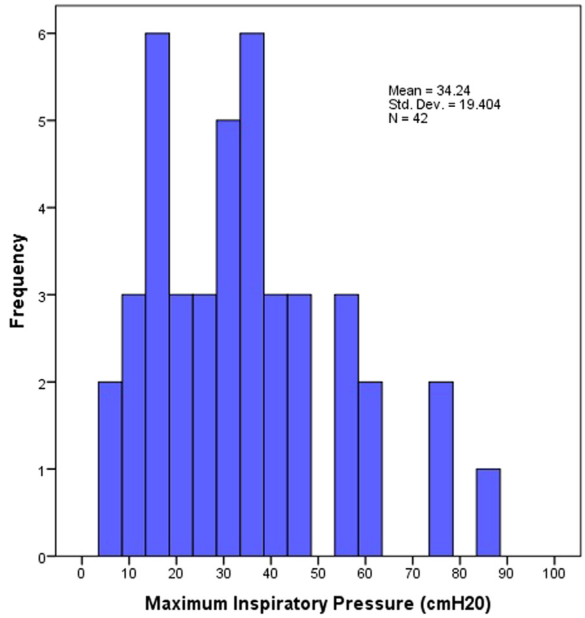

Fig. 3. Frequency distribution of Maximum Inspiratory Pressure (cm H_2O).

of ventilation, rather than following weaning. This early change would be consistent with clinical studies showing proteolysis occurring within 69 h of controlled ventilation[1] and recent physiological studies demonstrating reduced muscle fiber cross-sectional area and reduced protein to DNA ratios (29%) in skeletal muscles within the first 3 days of ICU admission.[17]

However, the fact that the relatively longer duration of ventilation in our group (mean 10.5 days) did not result in lower FRI scores is in contrast with the finding by Chang et al that FRI is negatively correlated with duration of ventilation ($r = -0.65$, $p = 0.007$). In the present study there was only a non-significant negative association between FRI and duration of ventilation ($r = -0.20$, $p = 0.20$). This may be explained by the predominance of spontaneous modes (e.g. pressure-support ventilation) used in the current study (see Table 1), whereas patients in Chang's cohort were predominantly ventilated using controlled methods.

It is not surprising that RPE scores at rest were strongly correlated with RPE scores during exercise. A patient feeling short of breath at rest is highly likely to feel more exertional distress when they exercise as the metabolic demand for oxygen increases. In this study, 40% of patients reported an RPE greater than zero at rest indicating an elevated work of breathing. However it was unexpected that RPE scores were only weakly correlated with fatigue resistance or functional scores, as we expected that poor inspiratory fatigue resistance would manifest as increased perceived exertion as the work of breathing increases during exercise. It is possible that some subjects have difficulty using the Modified Borg Scale to rate their perceived exertion and dyspnea, or that the scale is insufficiently sensitive to detect relationships at this level. However to our knowledge there is no other readily available standardized tool to measure perceived exertion or dyspnea in this context. The development of a sensitive standardized tool to measure exertion in critically unwell patients could be helpful in future.

The lack of correlation between MIP and function could also partly be explained by deficits in motor control. While inactivity leads to early muscle proteolysis, it is highly likely that inactivity also affects neural programming. In studies of specific inspiratory muscle training, early apparent improvements in MIP scores (e.g.

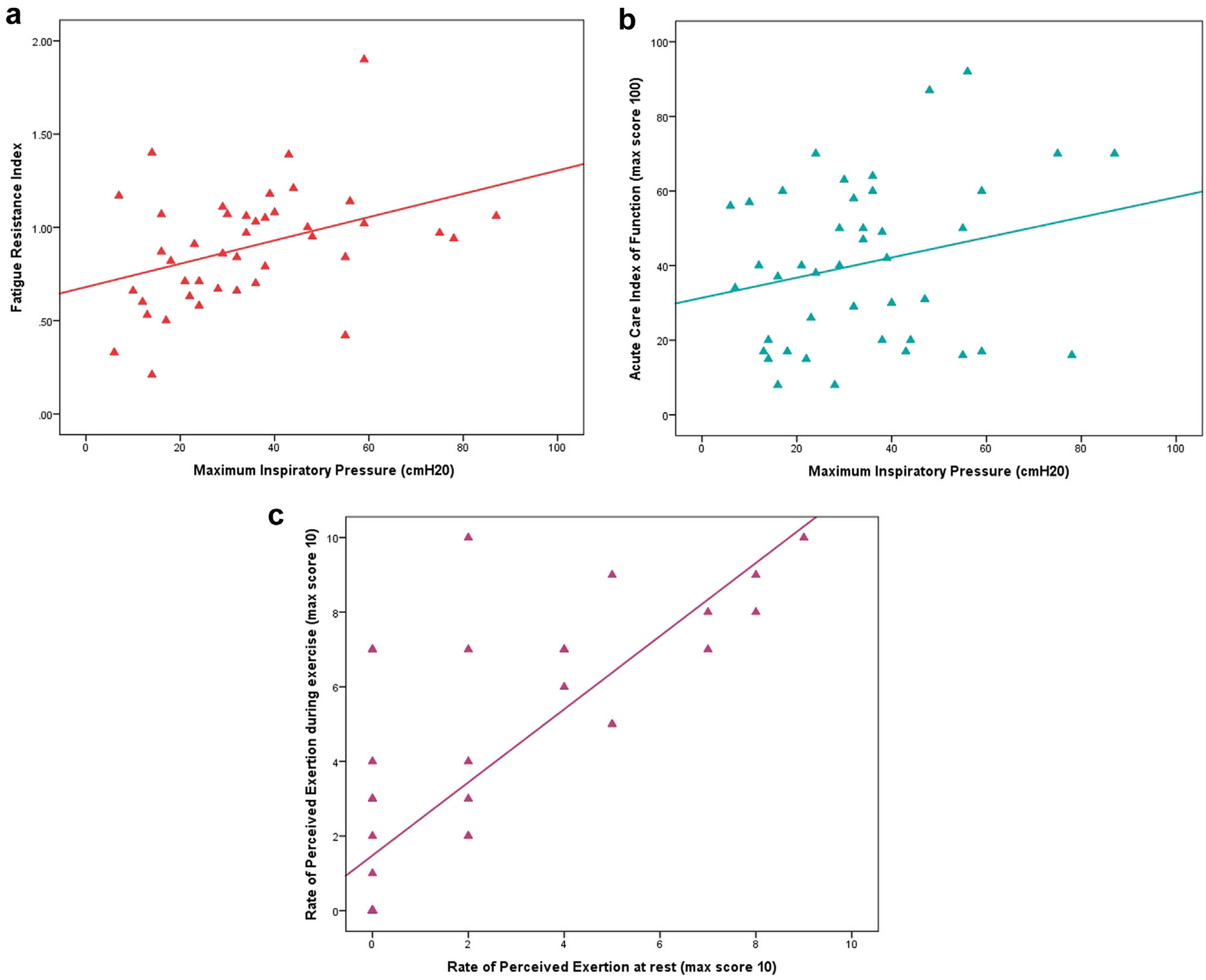

Fig. 4. Correlations between measures: a) between MIP(cmH_2O) and FRI scores. b) between MIP(cmH_2O) and ACIF scores. c) between RPE scores at rest and during exercise.

within 2 weeks of training) could be attributed to more efficient motor programming[18] rather than muscle hypertrophy. Thus it is likely that there is not a simple linear relationship between strength and function, and neural factors should be considered in future studies.

As 60% of patients in this study rated their perceived exertion as zero during exercise, it is also possible that 'peak exercise' (e.g. mobilization with assistance away from the bed space) was of insufficient intensity to challenge inspiratory muscles. If these recently weaned patients do not perceive any raised exertion, the training intensity may be inadequate. Even in an ICU where early mobilization is the standard of care, we may be yet to determine the limitations of exercise in the critically ill. However, the patient's perceived exertion is likely to be an important determinant of exercise capacity. In athletes working at peak exercise, exercise performance can be limited by the perception of exertion, even in the absence of peripheral biomarkers of fatigue.[5] The evidence that this perception of exertion is modifiable in athletes with training of the respiratory muscles may also have implications for recently weaned intensive care patients. It is possible that the 37% of patients demonstrating reduced FRI in this study may benefit from targeted training of their inspiratory muscles. IMT can hasten weaning in older ICU patients[19] but to our knowledge this remains uninvestigated in the post-weaning period. This is an important area of future research.

Table 3
Correlations between variables (Pearson r).

	ACIF	MIP	FRI
RPE (rest)	$r = -0.17$	$r = -0.18$	$r = -0.12$
	$p = 0.28$	$p = 0.27$	$p = 0.46$
RPE (exercise)	$r = -0.11$	$r = -0.15$	$r = -0.14$
	$p = 0.95$	$p = 0.37$	$p = 0.39$
APACHE II	$r = 0.05$	$r = -0.12$	$r = -0.79$
	$p = 0.77$	$p = 0.44$	$p = 0.62$
Duration of ventilation	$r = -0.10$	$r = -0.45$	$r = -0.20$
	$p = 0.51$	$p = 0.77$	$p = 0.20$

The limitations of this study include the fact that these results may be valid only for intensive care patients who have been weaned in a unit where minimal sedation and early mobilization are the norm. It is plausible that FRI, MIP and ACIF scores would differ considerably in patients undergoing deep sedation and bed rest as early deep sedation independently delays extubation and increases mortality.[20] Furthermore, the failure to find correlations between these variables may be attributable to the relatively small sample size, although this study was larger than previous studies.[4]

Despite these limitations, the consistency of the primary measure (FRI) with previous studies confirms that impaired fatigue resistance is detectable in at least a third of intensive care patients within the first few days following weaning. These results have implications for all clinicians working with ICU patients in the immediate post-weaning period. Medical and nursing staff can reassure patients that it is common to experience raised perceived exertion following weaning, even at rest, as this is a foreseeable consequence of prolonged mechanical ventilation. As dyspnea is complex and multifactorial in weaning from mechanical ventilation,[3] the psychological benefits of acknowledgment and reassurance may be important for the patient's experience.

Furthermore, clinicians should be aware that recently weaned patients may report high RPE levels during exercise, particularly if RPE is raised at rest. However, in our experience, raised RPE is not necessarily a barrier to participation in early rehabilitation in ICU and physiotherapists and nurses can work together to optimize patients' exercise capacity even in the presence of inspiratory muscle weakness.

Conclusion

In ICU patients recently weaned from mechanical ventilation of duration 7 days or longer, impaired respiratory endurance is detectable in one third of patients. Impaired respiratory muscle endurance is associated with inspiratory muscle weakness. Inspiratory muscle weakness does not appear to be closely associated with functional measures or perceived exertion 48 h following successful weaning in an ICU where early mobilization and minimal sedation are the standard of care.

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