Differences in the degree of respiratory and peripheral muscle impairment are evident on clinical, electrophysiological and biopsy testing in critically ill adults: a qualitative systematic review

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ABSTRACT

Background: Critically ill patients are exposed to a combination of insults that affect both respiratory and peripheral skeletal muscle function. However, different muscle groups may not be affected to the same extent by a prolonged critical illness.

Objective: To review original observational studies that measured an aspect of respiratory and peripheral muscle function in adults in the intensive care setting.

Design: Systematic review strategy and qualitative data synthesis.

Data sources and review methods: Four major citation databases were searched. Search terms included intensive care, critical care, diaphragm, quadriceps, and skeletal, respiratory and limb muscle. Titles and abstracts were reviewed to identify studies that measured both respiratory and peripheral muscle function. Reference lists of suitable publications were screened. Studies sampling critically ill patients with a neurological condition were excluded.

Results: 1119 items were identified, and 19 full-text/abstract publications were reviewed. Ten studies investigated patients with a critical illness-related neuromuscular disorder. Nine studies targeted septic patients with multiple organ failure or patients requiring prolonged mechanical ventilation. Clinical, electrophysiological and muscle biopsy specimen data were collected at different time-points and milestones relating to alertness, weaning criteria, respiratory support reduction and extubation.

Conclusions: Currently available bedside methods of measuring respiratory and peripheral muscle function in critically ill patients are somewhat inadequate. Yet there is evidence suggesting that respiratory muscles may be relatively spared from the damage that can occur as a result of immobility, prolonged mechanical ventilation and systemic inflammation in critical illness.

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Intensive care unit acquired weakness (ICUAW) is a diagnosis of exclusion based on both history of presentation and clinically detectable weakness. Diagnostic criteria have been recently proposed for ICUAW.[1] Abnormalities in neuromuscular electrophysiology and/or muscle histology can exist without clinically detectable weakness in ICU patients. However, when present with ICUAW, the classifications of critical illness polyneuropathy (CIP), critical illness neuromyopathy and critical illness myopathy may be applied.[1] The use of these terms in existing literature may not conform to the suggested framework, as prior to this nomenclature and diagnostic clarification, these terms (among many others) were used to describe critical illness-related neuromuscular disorders.

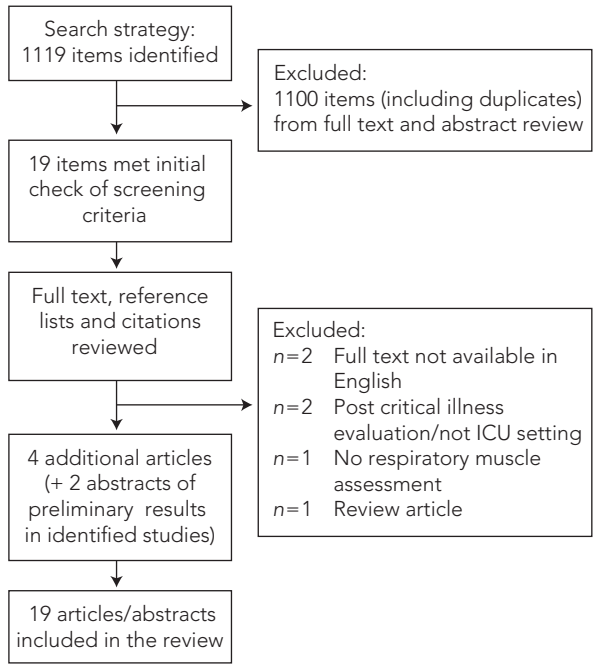
From the earliest electrophysiological studies of critically ill patients with CIP, critical illness neuromyopathy and critical illness myopathy, abnormalities have been identified in the phrenic nerve, diaphragm and accessory respiratory muscles, as well as peripheral muscles and nerves.[2-5] Subsequent research has primarily focused either on the role of the diaphragm in weaning from mechanical ventilation,[6] or the relationship between peripheral muscle dysfunction in critical illness neuromuscular disorders and prolonged weaning.[7-10] Despite recognition that both respiratory and peripheral muscle is involved, there have been few occasions where both types of muscle groups have been assessed in the same patients.

People who experience a critical illness are commonly exposed to an extended duration of mechanical ventilation, immobility and an increased risk of infection, resulting in lengthy periods of health care utilisation and potential long-term impairment. However, different skeletal muscle groups may not be affected uniformly by the combination of insults that occur during critical illness. This particularly applies to muscles involved with respiratory and locomotive functions.

Differential patterns of muscle dysfunction have been described in stable chronic conditions, including chronic obstructive pulmonary disease,[11] asthma,[12] chronic heart failure[13] and cystic fibrosis.[14,15] Understanding the unique elements of a dysfunctional pattern has enabled targeted rehabilitation programs to be developed that address muscular strength, local muscle endurance, aerobic endurance, respiratory muscle function, and flexibility issues that relate to a particular condition.

Similar principles may apply to critically ill patients. There has been an increase in the volume and quality of research investigating the efficacy of various exercise regimes in

Figure 1. Flow of studies through review process



ICU = intensive care unit.

clinical subgroups, with programs commencing soon after ICU admission or the institution of mechanical ventilation.[16-18] This research is generally supportive of the practice, which has been demonstrated to be safe to conduct[19,20] and to reduce morbidity.[21,22]

Opportunities to develop innovative rehabilitation regimes and optimise exercise programs are currently limited by existing knowledge about the interaction between the respiratory and peripheral muscles in critical illness. Furthermore, a need has been identified for clinical studies to investigate the involvement of the respiratory neuromuscular system in ICUAW and correlate it with dysfunction of the limbs.[23]

As there is a lack of clinical studies in this area, our aim in this review is to summarise current knowledge about the comparative deficits in respiratory and peripheral muscle in critically ill patients.

Methods

Data sources and searches

The Scopus, PubMed, Ovid MEDLINE and Cumulative Index to Nursing and Allied Health Literature (CINAHL) major citation databases were searched, without date restriction, up to August 2009. The key search terms included respiratory and limb muscle, intensive care, critical care, diaphragm and quadriceps, skeletal muscle, maximal inspiratory pressure, and leg muscle. For studies meeting the selection criteria, reference list screening, together with use of the "cited by" function in the Scopus database, enabled further searching for potentially relevant articles.

Study selection

The title and abstract (where available online) of the search results were screened to find original publications of observational studies. Review, comment and editorial articles were not included. Furthermore, no existing review article was found to address the topic of our review. Studies included for a full-text appraisal were those that met the following specific criteria:

- a respiratory muscle (either diaphragm or accessory) and a peripheral muscle were evaluated;
- the study related to an intensive/critical care setting/population;
- the study was an adult human study; and
- a full text of the publication was available in the English language.

Studies primarily sampling critically ill patients with a neurological condition were excluded.

Data extraction and quality assessment

Data were extracted in a narrative form according to the study design, sample characteristics, measures of peripheral muscle, measures of respiratory muscle and other relevant outcomes. We have included results where the presentation of the analysis was sufficiently detailed for this, where statistically significant results were found, or where results were relevant to the review question (statistically insignificant results are identified as such).

The quality of studies (excluding abstracts) was independently assessed with the Methodological Quality Instrument (MQI).[24] This scale was chosen because it gave a summary numerical score, it was developed specifically for critical appraisal, and it was suitable to use with the spectrum of non-experimental designs evaluated in our review.[25]

Data synthesis and analysis

We performed a final qualitative synthesis of the reviewed articles to assess whether there was a differential pattern of skeletal muscle dysfunction between respiratory and peripheral limb muscles in critically ill patients.

Results

Our search strategy yielded a total of 1119 items (including duplicates) for further review, which was reduced to 19 for the final data extraction and synthesis (Figure 1).

The study design and sample characteristics are presented in Table 1 and Table 2. Publications that used

Table 1. Summary of design characteristics of included studies

Reference	Design*	Control group	Sample size	Mean/median age in years (range)†	Sampling method	Inclusion criteria	Exclusion criteria	MQI score‡
Agten et al[26] 2009	P, CrS§	No	17	ns	Convenience	ns	ns	na
Caruso et al[27] 2008	P, Coh¶	No	116	Median 66 (range, 15–90)	Consecutive	MV > 72 hours	Flail chest, CAD, alveolar haemorrhage, low MAP after volume resuscitation	0.806
De Jonghe et al[28] 2007	P, CrS¶	No	116	Median 64 (IQR, 52–77)	Consecutive	MV ⩾ 7 days, met awakening criteria	PNS disease, bihemispheric or brainstem lesion	0.848
Klaude et al[29] 2007	P, CC, two study arms	Yes (n = 10)**	10	Median 67 (range, 40–80)	Convenience	Septic shock on admission, MV	Pre-existing neuromuscular disease, COPD, severe coagulopathy	0.806
Fredriksson et al[30] 2006	P, CC	Yes (n = 10)**	10	Median 67 (range, 40–80)	Convenience	ns	Pre-existing neuromuscular disease, COPD, severe coagulopathy	0.897
Magda et al[31] 2006	P, CS	No	1	Age 31 (n = 1)	Convenience	ns	ns	0.667
Fredriksson et al[32] 2005	P, CC§	Yes (n = 10)**	10	ns	ns	MV	ns	na
Bruton et al[33] 2002	R, CS	No	2	Ages 68, 19 (n = 2)	Convenience	MV > 2 weeks, willing to participate	Cardiovascular instability	0.783
Latronico et al[34] 1999	R, CS	No	5	Mean 36 (range, 19–72)	Convenience	ARF at planned ICU discharge, axonal polyneuropathy and myopathy	ns	0.630
Sander et al[35] 1999	R, Coh	No	102	ns	Systematic	Motor NCS and EMG on two extremities, diaphragmatic needle EMG	ns	0.690
Zifko et al[36] 1998	P, CrS	Yes (n = 25)††	62	Mean 63 (range, 4–84)	Convenience	CIP	ns	0.903
Watson et al[37] 1997	P, CrS§	Yes††	10	Median 70 (range, 45–81) quadr; median 62 (range, 40–74) diaphr	Convenience	ns	ns	na
Maher et al[38] 1995	R, CrS	Yes†† (limb [n=95]; resp [n=25])	40	Mean 66 (range, 18–84)	Convenience	Failure to wean criteria	Pre-existing neuromuscular disorder, tracheostomy	0.806
Witt et al[39] 1991	P, Coh	Yes (n = 95)††	43	Mean 64 (range, 21–78)	Consecutive	MV ⩾ 5 days, sepsis and MOF	Pre-existing peripheral neuropathy	0.889
Zochodne et al[2] 1987	R, CC¶	Yes‡‡	19	Mean 64 (range, 19–81)	ns	Referral for electrophysiological examination for failure to wean from MV	ns	0.852
Bolton et al[5] 1986	P, Coh	Yes‡‡	15 (resp [n = 10])	Mean 65 (range, 49–83)	Consecutive	CIP	ns	0.677
Zochodne et al[3] 1985	R, Coh§	No	9	ns	ns	ns	ns	na
Bolton et al[4] 1984	P, CS	No	5 (resp [n = 1])	66§§	Convenience	ns	ns	0.652
Gertz et al[40] 1977	P, CrS	Yes (n = 12)¶¶	12	Mean 66 (range, 46–75)	Convenience	ns	ns	0.759

ARF = acute respiratory failure. CAD = coronary artery disease. CIP = critical illness polyneuropathy. COPD = chronic obstructive pulmonary disease. diaphr = diaphragm. EMG = electromyography. HIV = human immunodeficiency virus. ICU = intensive care unit. IQR = interquartile range. MAP = mean arterial pressure. MOF = multiple organ failure. MQI = Methodological Quality Index. MV = mechanical ventilation. na = not applicable. NCS = nerve conduction studies. ns = not specified. PNS = peripheral nervous system. quadr = quadriceps. resp = respiratory data.

* Study design: P = prospective, Coh = cohort, CrS = cross-sectional, CC = case-controlled, CS = case study, R = retrospective. † Data for age were taken directly from the papers reviewed. Generally mean or median (+ range) were reported. ‡ Total points were divided by the total possible points (the sum of the maximum points for each item, except "na" items) to yield a fraction between 0 and 1. A score of 1 represented the highest quality.[24] § Abstract only. ¶ Sample taken from multiple ICUs/hospital centres. ** Control group of age- and sex-matched elective surgical cases.[29,30] These studies used abdominal surgical controls, median age (years) = 67 (range, 45–87). †† Normative mean values from healthy/laboratory control subjects, ages representing the third to eighth decades. ‡‡ Control group described as age- and sex-matched. §§ Age of the one subject who had respiratory and peripheral muscle assessment. ¶¶ Control group described as unmatched hospitalised patients, mean age (years) 62 (range, 48–78).

Table 2. Summary of sample characteristics of included studies

Reference	Sample characteristics	Severity of illness*	Marker of when assessment(s) completed
Agten et al[26] 2009	MV, died in ICU	ns	ns
Caruso et al[27] 2008	% of ICU days with SIRS = 93.6% (range, 14%–100%); indications for ventilation: ARF (59.4%), decreased consciousness (25.9%), haemodynamic instability (11.2%)	APACHE II = 19 (range, 6–34)	Daily MIP, MRC after extubation once awakening and comprehension confirmed: mean 8 (range, 3–26) days in protocol
De Jonghe et al[28] 2007	Septic shock (50%), pneumonia (24.1%), catecholamine use (74.1%), corticosteroid use (62.9%)	SAPS II = median 46 (IQR, 36–58)	Days from intubation to awakening and clinical assessment: median 10 (IQR, 8–14)
Klaude et al[29] 2007	MOF	SOFA = median 6 (range, 4–11) at time of biopsy	ICU LOS (days): median 8 (range, 2–22)
Fredriksson et al[30] 2006	MV, sepsis, MOF	SOFA = median 6 (range, 4–11) at time of biopsy	ICU LOS (days): median 8 (range 2–22)
Magda et al[31] 2006	ILD, use of MV, sedative, NMBA and corticosteroids†	ns	Biopsy 1 year prior to death and postmortem
Fredriksson et al[32] 2005	ns	ns	ns
Bruton et al[33] 2002	68-year-old with ARF after right upper lobectomy; 19-year-old with CAP/Goodpasture syndrome; both with depression and infections	ns	Assessed once respiratory support reduced, repeat measures 1–2 occasions per week
Latronico et al[34] 1999	Diagnoses: trauma, acute pancreatitis, pleural effusion, HIV, sepsis ($n = 5$), MOF ($n = 4$), pneumonia ($n = 3$), ARDS ($n = 2$); MV 11–56 days; ICU LOS 12–60 days†	ns	Days after planned ICU discharge: 0–3 (respiratory), 1–6 (electophysiological)
Sander et al[35] 1999	ns†	ns	ns
Zifko et al[36] 1998	SIRS; ICU admission category: surgical (50%), sepsis (29%), trauma (8%), other (13%); mean days of MV = 58 (range, 9–251)†	ns	Days after ICU admission: mean 40 (range, 7–240)
Watson et al[37] 1997	ns	ns	ICU LOS (days) at diaphragm assessment: mean 35 (range, 6–97); at quadriceps assessment: mean 27.5 (range, 7–59)
Maher et al[38] 1995	Variety of conditions necessitating MV, polyneuropathy (total $n = 33$): subgroups CIP ($n = 25$), GBS ($n = 2$), diabetes and CIP ($n = 4$), uraemia and CIP ($n = 2$)†	ns	Days of MV: mean 14 (range, 1–108)
Witt et al[39] 1991	Main diagnosis: lung condition (23%), surgical (21%), trauma (16%), sepsis (14%)†	ns	Inclusion criteria met, days after ICU admission: mean 28 (range, 5–89)
Zochodne et al[2] 1987	CIP diagnosis: electrophysiological ($n = 17$), postmortem ($n = 2$); MV, sepsis, MOF, organ system dysfunction: pulmonary (79%), cardiac (68%), hepatic (47%), renal (16%)†	ns	Days after ICU admission: mean 32 (range, 6–87); days after hospital admission: mean 4 (range, 0–24)
Bolton et al[5] 1986	Sepsis, variety of primary illnesses, MV on ICU admission, minimum of two dysfunctional organ systems†	ns	Within 1 month of hospital admission, follow-up 1–6 months
Zochodne et al[3] 1985	Sepsis, MOF, MV, clinically weak, areflexive, electrophysiological evidence of motor and sensory polyneuropathy before death†	ns	Postmortem
Bolton et al[4] 1984	ARF, COPD, sepsis, MV†	ns	Weeks after ICU admission: 5; necroscopy after death at 3 months
Gertz et al[40] 1977	Acute exacerbation of COPD, assisted ventilation and MV at admission ($n = 2$), total using MV ($n = 4$)	ns	Day 1 of ICU admission, after 6–8 weeks of treatment

APACHE II = Acute Physiology and Chronic Health Evaluation II. ARDS = acute respiratory distress syndrome. ARF = acute respiratory failure. CAP = community-acquired pneumonia. CIP = critical illness polyneuropathy. COPD = chronic obstructive pulmonary disease. GBS = Guillain-Barré syndrome. HIV = human immunodeficiency virus. ICU = intensive care unit. ILD = interstitial lung disease. IQR = interquartile range. LOS = length of stay. MIP = maximal inspiratory pressure. MOF = multiple organ failure. MRC = Medical Research Council strength grading scale. MV = mechanical ventilation. NMBA = neuromuscular blocking agent. ns = not specified. SAPS II = Simplified Acute Physiology Score version II. SIRS = systemic inflammatory response syndrome. SOFA = Sequential/Sepsis-related Organ Failure Assessment score.

* Data presented are median (range), unless otherwise indicated. † Study made a critical illness neuromuscular disorder diagnosis according to electrophysiological and/or tissue biopsy findings.

normative data for comparison with ICU subject results did not give references for the normative data sets used. The duration of mechanical ventilation was specifically described in 18 of the 19 studies, the exception being the study by Watson et al.[37] Where ICU length of stay was used to mark the time when the respiratory and peripheral muscle examinations occurred, it was implied that mechanical ventilation was continued over at least this period. The duration of complete immobility prior to data collection was not stated, although the publications imply this to be the duration of mechanical ventilation.

Ten studies sought to specifically investigate patients with critical illness neuromuscular disorders that were diagnosed according electrophysiological and/or tissue biopsy findings, but only two of these documented a clinical assessment of muscle strength.[34,36] The remaining nine studies specifically targeted septic critically ill patients with multiple organ failure or patients requiring prolonged mechanical ventilation. Two of the studies used the Medical Research Council muscle strength sumscore to diagnose ICUAW.[27,28]

Respiratory and peripheral muscle examinations were performed at a variety of time-points. According to admission characteristics, this ranged from the point of ICU admission to the point of ICU readmission. Clinical milestones were also used in an attempt to standardise a common examination point. These included level of alertness, weaning criteria, respiratory support reduction, extubation and time of clinical referral. This was particularly evident in the cross-sectional studies. Ten studies specifically stated (to within a day) the time when muscle examination occurred. These examinations were found to have occurred between 1 and 240 days of the various time-points or clinical points described, and the minimum examination time was commonly within 7 days.

Table 3. Methods and results from studies that used clinical measures

Reference	Peripheral	Respiratory
Caruso et al[27] 2008	MRC summated score ($n = 116$): median 46 (range, 0–60); no difference or correlation between MRC score and patients with increasing or decreasing MIPuni trend	MIPuni trend over duration of MV, independently predicted by level of sedation
De Jonghe et al[28] 2007	MRC summated score ($n = 115$): median 41 (IQR, 21–52); correlation with MIP rho = 0.31 ($P = 0.001$); MEP rho = 0.49 ($P < 0.0001$); VC rho = 0.31 ($P = 0.007$)	MIP: $n = 79$; median (IQR) = 30 (20–40) cmH_2O; MEP: $n = 78$; median (IQR) = 30 (20–50) cmH_2O; VC: $n = 73$; median (IQR) = 11.1 (6.3–19.8) mL/kg
Bruton et al[33] 2002	Grip strength (in Newtons): baseline 58N and 83N; final 182N and 163N	Peak MIP: baseline 42 cmH_2O and 35 cmH_2O; final 70 cmH_2O and 47 cmH_2O; Sustained MIP: baseline 38 cmH_2O and 14 cmH_2O; final 188 cmH_2O and 269 cmH_2O

IQR = interquartile range. MEP = maximal expiratory pressure. MIP = maximal inspiratory pressure. MIPuni = MIP using the unidirectional valve method. MRC = Medical Research Council strength grading scale. MV = mechanical ventilation. VC = vital capacity.

Table 4. Methods and results from studies that used clinical and electrophysiological measures

Reference	Peripheral	Respiratory
Latronico et al[34] 1999	MRC: gross score = 3 ($n = 3$), 4 ($n = 1$), arm 5 and leg 3 ($n = 1$); EMG: used to diagnose CIP	VC: reduced in all subjects PiMax and PeMax: $n = 3$, PiMax reduced to a greater extent than PeMax, according to normal reference values
Zifko et al[36] 1998	MRC: grade $\leqslant 3$ distally in 43% of sample, $\leqslant 3$ proximally in 40%, 4 in distal groups in 24%, 4 in proximal groups in 27%, normal strength in 5% No correlation with ICU length of stay or duration of MV NCS: CMAP amplitude abnormal in all subjects EMG: high frequency of fibrillation potentials and positive sharp wave forms in biceps 48%, interossei 66%, vastus medialis 68%, tibialis anterior 69%, prolonged motor unit potentials in $\geqslant 82\%$ of subjects	Bilateral phrenic NCS: phrenic nerve latencies or abnormal diaphragm CMAP in 77% of patients Diaphragm EMG: high frequency of fibrillation potentials and positive sharp wave forms in 5% of sample, mild to moderate abnormalities in 24%, total incidence of diaphragm abnormalities 29%, reduced number of diaphragm motor units in 47%

CIP = critical illness polyneuropathy. CMAP = compound motor action potential. EMG = electromyography. ICU = intensive care unit. LOS = length of stay. MRC = Medical Research Council strength grading scale. PeMax = maximal expiratory pressure. MV = mechanical ventilation. NCS = nerve conduction studies. PiMax = maximal inspiratory pressure. VC = vital capacity.

Table 5. Methods and results from studies that used electrophysiological measures

Reference	Peripheral	Respiratory
Sander et al[35] 1999	NCS and EMG: $n = 44$ (43%) with CIP	Diaphragm EMG: $n = 24$ (55%) with CIP + diaphragm denervation ($n = 15$ with other causes, $n = 9$ with CIP-related dysfunction), $n = 13$ no CIP + diaphragm denervation
Watson et al[37] 1997	Femoral nerve magnetic stimulation: median quadriceps twitch tension force = 27% of normal mean value	Phrenic nerve magnetic stimulation: median transdiaphragmatic twitch pressure = 38% of normal mean value
Maher et al[38] 1995	NCS and EMG: $n = 25$ with CIP, association between limb polyneuropathy and abnormal phrenic nerve conduction/diaphragm denervation (Cramer's V = 0.45)	Chest wall and diaphragm EMG with phrenic NCS: $n = 14$ (56%) had CIP + respiratory involvement, $n = 13$ with unilateral/bilateral phrenic neuropath, $n = 1$ with denervated chest wall muscles with normal phrenic nerve)
Witt et al[39] 1991	EMG and NCS to generate nerve function index score: abnormal peripheral function in 70% of subjects, negative correlation with ICU length of stay prior to first examination ($r^2 = 0.4254$)	Phrenic NCS and diaphragm EMG: positive correlation between nerve function index and phrenic nerve CMAP amplitude (in $n = 29$) ($P = 0.009$)
Bolton et al[5] 1986	NCS: reduced CMAP amplitude of peripheral motor nerves with only mildly abnormal F wave latencies EMG: acute denervation peripherally	External oblique and intercostal EMG: positive F waves and fibrillations in external intercostal and oblique in 4/12 subjects with severe CIP Phrenic NCS: phrenic nerve F wave latencies were not significantly prolonged; absent response to phrenic nerve conduction over diaphragm in 3/10 subjects with severe CIP

CIP = critical illness polyneuropathy. CMAP = compound motor action potential. EMG = electromyography. ICU = intensive care unit. NCS = nerve conduction studies.

Table 6. Methods and results from studies that used electrophysiological and muscle biopsy measures

Reference	Peripheral	Respiratory
Bolton et al[4] 1984	NCS: severe motor and sensory polyneuropathy due to axonal degeneration EMG: widespread denervation Peripheral biopsy: extensor hallucis longus and quadriceps denervation atrophy, variability in fibre size, cytoarchitectural disorganisation Postmortem biopsy: denervation atrophy of all groups, severe grouped atrophy of type I and type II fibres	Bilateral phrenic NCS: absent phrenic nerve response External oblique and intercostal EMG: denervation including external oblique and intercostal Intercostal biopsy: intercostal denervation atrophy, variability in fibre size, cytoarchitectural disorganisation Postmortem intercostal and diaphragm biopsy: denervation atrophy of both muscles, severe grouped atrophy of type I and type II fibres
Zochodne et al[2] 1987	NCS: thenar and extensor digitorum brevis CMAP amplitude reduced by > 50% compared with controls in all CIP subjects, significant difference between mild and severe CIP patients in thenar CMAP amplitude EMG: significant difference between mild and severe CIP subgroups and the frequency of positive wave and fibrillation potentials in quadriceps Postmortem biopsy: acute and chronic denervation atrophy in distal and proximal muscle groups	Phrenic NCS: normal phrenic nerve conduction in $n = 6$, absent phrenic CMAP in $n = 2$ (severe CIP) Chest wall EMG: abnormal activity in intercostal and external oblique of $n = 13$ Postmortem intercostal and diaphragm biopsy: intercostal atrophy in 8/9 patients, diaphragm atrophy in 4/9 patients, total of 8/9 patients with non-specific respiratory muscle denervation atrophy

CIP = critical illness polyneuropathy. CMAP = compound motor action potential. EMG = electromyography. NCS = nerve conduction studies.

Measurement methods

Both volitional and non-volitional methods were used to evaluate respiratory and peripheral muscle function. However, the studies can be better classified according to measurement method, as clinical (Table 3), clinical and electrophysiological (Table 4), electrophysiological only (Table 5), electrophysiological and muscle biopsy specimen (Table 6), and muscle biopsy specimen only (Table 7). Most nerve conduction studies evaluated both motor and sensory nerves, but only the motor nerve findings are reported here.

Peripheral and respiratory muscle assessments

Results from the peripheral and respiratory muscle assessments for each study are presented in Tables 3–7. In relation

Table 7. Methods and results of studies that used muscle biopsy measures

Reference	Peripheral	Respiratory
Agten et al[26] 2009	Postmortem quadriceps biopsy: inflammation	Postmortem diaphragm biopsy: higher myogenin mRNA (171%) and IB– (32%; $P = 0.051$) expression, lower MURF-1 (–76%; $P < 0.05$) and MAFbx (–80%; $P = 0.08$) mRNA expression, unchanged MyoD mRNA, in diaphragm compared with quadriceps
Magda et al[31] 2006	Biopsy: biceps atrophy in 50%–60% of fibres, angulated fibres with increased number of internal nuclei, predominantly type II fibres but with increased lipid droplets Postmortem biopsy: widespread TFL, angulated fibres with core-like lesions in peripheral muscle	Biopsy: consistent with polymyositis with predominant inflammatory involvement of respiratory muscles Postmortem intercostal and diaphragm biopsy: TFL sparing in diaphragm and relative sparing of intercostals, fewer abnormalities in intercostal and no abnormality in diaphragm
Klaude et al[29] 2007	Vastus lateralis biopsy: proteasome activity in septic patients was 45% higher than in controls	Serratus anterior biopsy: proteasome activity was 30% higher in septic patients than controls
Fredriksson et al[30] 2006	Vastus lateralis biopsy: no difference in citrate synthase levels in homogenate between groups; no difference in complex I and IV (expressed per citrate synthase activity) in isolated mitochondria between groups; SOD activity in isolated mitochondria was 411% higher in ICU patients than in controls; ICU patients had 40% lower ATP, 34% lower CrP and 34% higher lactate than controls	Intercostal biopsy: citrate synthase levels in homogenate were 53% lower in ICU patients than in controls; no difference in complex I and IV (expressed per citrate synthase activity) in mitochondria between groups; SOD activity in mitochondria was 230% higher in ICU patients than in controls; no difference in ATP, CrP and lactate concentrations in intercostal between groups; in healthy subjects ATP, CrP and lactate concentrations were lower in intercostal than leg; no difference in intercostal or leg muscle subsarcolemmal mitochondria morphology between groups
Fredriksson et al[32] 2005	Vastus lateralis biopsy: lower protein, with higher 26S proteasome, glutamine, phenylalanine and BCAA in ICU patients than in controls	Intercostal biopsy: no difference in protein or BCAA levels between ICU patients and controls, higher 26S proteasome and phenylalanine, with lower glutamine in ICU patients compared with controls
Zochodne et al[3] 1985	Postmortem biopsy: denervation atrophy in all patients	Postmortem intercostal and diaphragm biopsy: grouped fibre atrophy in intercostals $n = 6$ and diaphragm $n = 4$
Gertz et al[40] 1977	Quadriceps femoris biopsy: ATP concentration (–20%) and CrP (–25%) were lower in patients on admission than in controls; lactate and glucose were increased at admission by 2.7–2.9 times compared with controls	Intercostal biopsy: ATP concentration was lower (–17% [NS]) on admission, and both lactate and glucose concentrations were about 1.8 times higher in patients on admission than in controls; no difference in CrP or glycogen on admission between patients and controls

ATP = adenosine triphosphate. BCAA = branched-chain amino acids. CrP = creatine phosphate. IB– = inhibitor proteins of the NF-kB pathway. ICU = intensive care unit. MAFbx = muscle-specific ubiquitin ligase atrogin-1. MURF-1 = muscle ring finger protein-1. NS = not statistically significant. SOD = superoxide dismutase. TFL = thick filament loss.

to outcomes, Zifko et al[36] reported a difference in the duration of mechanical ventilation (7 days) and ICU length of stay (4 days) in patients with CIP who had an abnormal diaphragm compound motor action potential (CMAP) on electromyography compared with those with a normal diaphragm CMAP. Maher et al[38] reported a difference in weaning time for CIP patients ($n = 12$) with phrenic neuropathy (mean, 56 days; range, 16–178 days) compared with those without phrenic neuropathy ($n = 13$) (mean, 33 days; range, 11–78 days). Zochodne et al[2] described a difference in the duration of mechanical ventilation required for patients with mild CIP (mean, 62 days) and those with severe CIP (mean, 74 days). However, none of the differences reported in these three studies were statistically significant. De Jonghe et al[28] found that low maximal inspiratory pressure ($\leqslant 30\,cmH_2O$), low maximal expiratory pressure ($\leqslant 30\,cmH_2O$) and low Medical Research Council sumscore (< 41) were independent predictors of delayed successful extubation in patients clinically diagnosed with ICUAW, and that each of these factors increased the risk of a successful extubation being delayed for 7 or more days after awakening (by 8.02, 4.14 and 3.03 times, respectively).

Conclusions on a differential pattern of dysfunction

In the observational studies reported, both respiratory and peripheral muscles were affected by a combination of factors, including mechanical ventilation, immobility, sepsis and multiple organ failure. In cases where peripheral neuromuscular dysfunction was identified, the respiratory muscles were not consistently involved. The 11 studies that presented sufficient data for a qualitative comparison showed that dysfunction in the respiratory muscles was less marked than that observed in the peripheral muscles (Table 8).

Table 8. Comparative effects of critical illness on respiratory and peripheral muscle dysfunction

Reference	Respiratory versus peripheral
Agten et al[26] 2009	Respiratory < peripheral
Caruso et al[27] 2008	—
De Jonghe et al[28] 2007	—
Klaude et al[29] 2007	Respiratory < peripheral
Fredriksson et al[30] 2006	Respiratory < peripheral
Magda et al[31] 2006	Respiratory < peripheral
Fredriksson et al[32] 2005	Respiratory < peripheral
Bruton et al[33] 2002	—
Latronico et al[34] 1999	—
Sander et al[35] 1999	Respiratory < peripheral
Zifko et al[36] 1998	Respiratory < peripheral
Watson et al[37] 1997	Respiratory < peripheral
Maher et al[38] 1995	Respiratory < peripheral
Witt et al[39] 1991	—
Zochodne et al[2] 1987	Respiratory < peripheral
Bolton et al[5] 1986	—
Zochodne et al[3] 1985	—
Bolton et al[4] 1984	—
Gertz et al[40] 1977	Respiratory < peripheral

Discussion

In this review we sought to establish evidence of a differential pattern of dysfunction between respiratory and peripheral muscles in patients with a critical illness. There appears to be a lower incidence of respiratory muscle involvement in the presence of critical illness related peripheral neuromuscular disorders. Increases in the duration of mechanical ventilation and length of ICU stay were noted in patients with respiratory involvement compared with those without. On the other hand, where there is respiratory involvement, there appears to be a relative sparing of these muscles, as detected by commonly used bedside methods. This is in conflict with the observation that complete inhibition of spontaneous diaphragm activity is associated with a reduction in its force-generating capacity in animal models,[41] and diaphragm atrophy in humans.[42] However, allowing intermittent periods of spontaneous diaphragm activity may attenuate loss of diaphragmatic force.[43] The modes of mechanical ventilation used in the reviewed studies were rarely stated.

This is the first review to examine the interaction between respiratory and peripheral muscle dysfunction in adult ICU patients. It highlights limitations in the existing literature and may assist subsequent research in this area.

The quality of reviewed studies appeared to be moderately high according to the MQI, but it was not possible to derive a summary judgement from this scale alone. This is a limitation of the MQI, as it is for any scale tool, along with variations in item inclusion and weighting between appraisal instruments.[25] There is no consensus on a single tool that should be used to appraise observational studies.[25,44] However, there are guidelines for assessing the quality of observational research.[45] The extent of narrative appraisal according to quality criteria in our review included providing information on sample characteristics, control groups, the measurement methods used and outcomes.[45] It would also be necessary to consider the aim of each included study, the completeness of the dataset, and distorting influences on the results and validity.

There was a lack of prospective studies of sufficient sample size, with a systematic method of sample selection, to allow a more convincing comment to be made on the effect of the critically ill condition on skeletal muscle dysfunction. In three of four suitable studies,[27,28,36,39] it was not possible to comment on a differential pattern of dysfunction.

Although difficult to achieve, there was poor control of factors that may affect muscle dysfunction, such as the period of immobility and duration of mechanical ventilation. This should have been possible to control in the studies using non-volitional measures, and of these, only the study by Witt et al[39] standardised the assessment timepoint. The duration of ICU stay at enrolment varied significantly, as the duration of mechanical ventilation and immobilisation was not standardised in any study that used a non-volitional measure of muscle function. As changes in muscle function may be time-dependent, such inconsistencies limit comparisons between studies.

The clinical implications of abnormal muscle morphology and electrophysiological responses in critical illness remain poorly understood. Our observations based on this review suggest that care should be taken not only to ensure that standardised analysis methods are used, but also to ensure that generalisations are not made from one muscle group to another. Intra-individual variation should also be considered, as demonstrated by Klaude et al,[29] who measured the variation in proteasome levels from vastus lateralis biopsies from the left and right legs of critically ill septic patients and controls.

Conclusions

Evidence of a difference in the degree of respiratory and peripheral muscle impairment on clinical, electrophysiological and biopsy testing in critically ill adults is limited by variations in both the methodological quality and ability to appraise the reviewed studies. A prospective study with a systematic sampling strategy, defined examination timepoint, and an adequately matched and described control

group is indicated to address this question. It is not known what the implications are of a differential pattern of skeletal muscle dysfunction in critical illness on the exercise prescription for these patients. There remains scope for other methods of measuring skeletal muscle dysfunction to be investigated and for integrating respiratory and peripheral muscle assessments in future research.

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