Title:

The management of respiratory problems in people with neurodegenerative conditions: a narrative review.

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Abstract

Background

Respiratory failure and dysfunction are problems common in many neurodegenerative conditions and although physiotherapists manage these problems, it is not known which treatments have been studied and the efficacy of those treatments.

Objective

The purpose is to review, using the PRISMA approach, evidence related to the management of respiratory problems in people with neurodegenerative conditions in order to provide evidence for physiotherapy practice.

Data sources

Comprehensive searches were conducted using the following electronic databases from inception to May 2010: HUGEnet, SIGLE, British Library Direct, CINAHL, Medline, AMED, and Web of Knowledge. Bibliographies of all studies and systematic reviews were searched by hand.

Study selection

Studies were selected based on: self ventilating participants with neurodegenerative conditions; interventions aimed at improving respiratory function; outcomes were any valid and reliable measures of respiratory function.

Study appraisal

Studies were appraised by one reviewer using the Critical Appraisal Skills Programme. Data was synthesised using a narrative approach.

Results

Thirty five studies were included in the review. The strongest evidence was for the use of non-invasive ventilation for people with amyotrophic lateral sclerosis, although this was weak. The evidence for the use of respiratory muscle training and methods to increase peak cough flow shows a positive effect, but is also weak.

Conclusion

There is weak evidence for the positive effects of physiotherapy interventions for respiratory problems in people with neurodegenerative conditions. Further work is necessary in specific neurodegenerative conditions to identify why respiratory problems occur and larger scale studies to investigate management of these problems.

Keywords

Neurodegenerative conditions; respiratory insufficiency; physiotherapy

Introduction

Rationale

Respiratory dysfunction is common in neurodegenerative conditions for example multiple sclerosis (1) amyotrophic lateral sclerosis (2) and Huntington's disease (3). Physiotherapy management of respiratory problems is often supportive rather than preventative, taking place only in the middle and late stages of the condition (4). With the exception of national guidelines for the use of non-invasive ventilation in people with motor neurone disease (5) there are no national guidelines for the management of respiratory problems in people with Parkinson's disease, Huntington's disease or multiple sclerosis. The BTS/ACPRC (6) guidelines for the adult, spontaneously breathing patient focuses on people with neuromuscular disease but does not provide sufficient detail for neurodegenerative conditions. Neurodegenerative conditions differ to neuromuscular disease in that the former refers to central neurological disorders, whereas neuromuscular refers to post neuromuscular junction disorders. Multiple sclerosis, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis/motor neurone disease (ALS/MND) are neurodegenerative with central nervous system processing problems and peripheral weakness.

People with neurodegenerative conditions have difficulties clearing secretions for a number of reasons; including respiratory muscle weakness and bulbar insufficiency (7). Ineffective gaseous exchange may occur due to retained secretions, compounded by respiratory muscle weakness affecting effectiveness of cough. Decreased inspiratory muscle strength may lead to alveolar hypoventilation, ventilation-perfusion mismatch and further respiratory muscle fatigue due to altered biomechanics (8). A gap in knowledge exists relating to the physiotherapy management of respiratory problems in people with neurodegenerative conditions, despite being the leading cause of death in this population (7)

Objective

The purpose of this paper is to review, using the PRISMA statement (9), evidence related to the management of respiratory problems in people with neurodegenerative conditions in order to influence physiotherapy practice.

Methods

Search process

A PICO (Population, Intervention, Comparison, and Outcome) approach was used (10, 11). The population was defined as people with neurodegenerative conditions. The intervention was any physiotherapy-based intervention influencing the respiratory system. No set comparisons were made or follow up times set. Outcome was any reliable and valid measure of respiratory function and not solely respiratory failure.

Comprehensive searches were conducted using the following electronic databases from inception to May 2010 (number of studies identified in brackets): HUGEnet (161), SIGLE (624), British Library Direct (192), CINAHL (130), Medline, EMBASE and AMED (4,307). Bibliographies of all studies and systematic reviews were searched by hand. Key words were structured using PICO. Population keywords included ‘neuro*’, ‘Parkinson’s disease’, ‘Amyotrophic Lateral Sclerosis’, ‘Motor Neurone Disease’, ‘Multiple Sclerosis’, and ‘Huntington’s disease’. Intervention keywords included ‘physiotherapy’ and ‘respiratory’ with outcome words included ‘lung’. Subsequent to the initial search and analysis of the categories of evidence found, two further search terms were used; respiratory muscle strength and retained secretions. See Figure 1 for the search strategy used in CINAHL, Medline, AMED and EMBASE databases.

Figure 1

Eligibility criteria, identification and selection of studies

Full text English language randomised controlled trials, experimental studies, prospective and retrospective observational studies which investigated changes in respiratory function following a physiotherapy-based intervention were included. One reviewer identified and reviewed all titles and abstracts followed by full text. Exclusion criteria were:

- Population solely neuromuscular conditions such as myesthenia gravis and muscular dystrophies;
- Population entirely aged less than 18;
- Population not spontaneously breathing;
- Intervention did not influence respiratory function;
- Sample n=1;
- Outcome measure solely respiratory failure;

Critical appraisal

Critical appraisal was carried out by one reviewer using the Critical Appraisal Skills Programme (CASP) appraisal tool (12).

Data analysis

Analysis was completed by one reviewer. Due to heterogeneity of populations, interventions and outcome measures it was not possible to carry out a meta-analysis. A narrative review was carried out of all included studies.

Results

Study selection

A total of 5,414 studies were retrieved with 5,368 being excluded by title, abstract or method, see Figure 2. Eleven studies were excluded by full text (available from authors on request).

Descriptive analysis of the remaining 35 studies highlighted three main themes: the problem of retained secretions, the problem of decreased muscle strength and the influence of exercise on respiratory function. Studies were grouped into these themes for the narrative review.

Figure 2

Critical appraisal

A summary of the critical appraisal, following the CASP approach (12), of all selected studies (n=35) is in Table 1. Populations were clearly defined in all studies; only two studies carried out power calculations. In those studies (n=6) that required allocation to groups, this was defined. Random allocation was defined in the seven randomised controlled trials (RCT). Reproducibility of interventions was variable (14/35 not reproducible), reasons including retrospective studies and inadequate information given. All outcome measures were defined, reliable and valid but in comparable studies, different outcome measures were used. Generalisability of the findings was low for the majority of studies due to lack of power and non-reproducible interventions.

Table 1

Study characteristics and synthesis of results

Based on descriptive analysis of selected studies, three main themes were identified; the problem of retained secretions (n=10), the problem of decreased respiratory muscle strength (n=19) and the influence of exercise on respiratory function (n=6). The theme of retained secretions was sub divided into interventions to improve cough effectiveness (n=7) and interventions to mobilise secretions (n=3). The theme of decreased respiratory muscle strength was subdivided into non-invasive ventilation (n=10) and respiratory muscle training

(n=9). The third theme included studies related to exercise. Details of study characteristics are summarised in Tables 2-5.

The problem of retained secretions

Ten studies (see Table 2) described intervention for retained secretions due to ineffective cough. All studies were small, populations were ALS/MND (n=6) and other neurodegenerative conditions (n=4). Six studies compared combinations of increasing maximal insufflation capacity (MIC), maximum insufflation-exsufflation (MIE) and manually assisted cough (MAC). Three studies used high frequency chest wall oscillation (HFCWO) as an intervention to mobilise secretions and one study investigated mechanical glottis to enhance cough. The primary outcome measure for most studies (7/10) was peak cough flow (PCF) with two using peak expiratory flow rate (PEFR) and one using forced vital capacity (FVC) and oxygen saturation (SaO_2).

Table 2

Studies relating to improvement of cough effectiveness

Winck *et al* 2004 (13) investigated the effects of mechanical insufflation-exsufflation on parameters including PCF, SaO_2, and dyspnoea. The sample was 13 subjects with ALS and 7 subjects with other neurodegenerative conditions. PCF and SaO_2 were measured at baseline and after MIE ±40 cmH_2O and showed a significant improvement in subjects with ALS ($p<0.005$ PCF and SaO_2) and other neurodegenerative conditions (PCF $p<0.05$, SaO_2 $p<0.005$). Dyspnoea was measured in the neurodegenerative conditions group and significantly decreased from baseline to ±40 cmH_2O ($p <0.05$). Median PCF increased from 180 to 220L/min in the ALS group and from 170 to 200L/min in the neurodegenerative condition group.

Bach 1993 (14), Chatwin *et al* (15) Mustfa *et al* 2003 (16) and Sancho *et al* 2004 (17) compared combinations of MIE, manual assisted cough (MAC) and breath stacking in people with ALS and other neurodegenerative conditions, using PCF as an outcome. For

patients with ALS (n = 73, (16, 17)), MIE was more effective than MAC in those patients without bulbar involvement and who are stable. MIE was not effective in those with bulbar dysfunction and those with little lung function impairment. The specific issue of bulbar involvement highlights the importance of impaired cough due to upper airway weakness which may not be overcome by these interventions (16). In people with other neurodegenerative conditions, Bach (14) found MIE more effective than MAC with breath stacking; cough with insufflations and unassisted cough. Chatwin *et al (15)* found that although MIE and exsufflation alone were better than unassisted cough, they were not significantly better than assisted cough, in a mixed adult and child sample. In a small study of 10 patients with neurodegenerative conditions, Trebbia *et al* (18) found a combination of MAC and manual hyperinflation significantly improved PCF.

An alternative aid to cough may be a mechanical glottis device that imitates glottis closure. Suleman *et al* (19) investigated the mechanical glottis in healthy controls and people with bulbar problems and demonstrated that the device created a PEFR significantly higher than that of both a straightforward PEFR manoeuvre and a cough manoeuvre, in people with bulbar problems.

Physiotherapy based interventions to improve cough effectiveness by increasing PCF have some efficacy for people with neurodegenerative conditions. Mechanical insufflation-exsufflation and manually assisted cough appear to be more effective than unassisted cough. The choice of intervention depends upon the patient's vital capacity and whether there is bulbar involvement. The heterogeneous populations used including neurodegenerative and neuromuscular disorders make it difficult to draw conclusions for specific disease populations.

Intervention to mobilise secretions

The above interventions focused on increasing flows necessary to expectorate secretions, whereas high frequency chest wall oscillation (HFCWO) aims to mobilise secretions. In three studies with a total of 62 patients with ALS, HFCWO was applied twice a day for 10-30

minutes per session (20-22). Although there were no significant changes in respiratory function (SaO_2, FVC, PCF), breathlessness decreased significantly (20) and 92% felt better after treatment (22). Based on this, HFCWO may enhance mobilisation of secretions in people with neurodegenerative conditions, but large scale studies are necessary to provide conclusive findings.

Summary of the problem of retained secretions

Studies on management of retained secretions have focused on increasing lung volumes to create flow rates sufficient to mobilise and expectorate secretions. Evidence suggests that improvements in PCF may be gained through maximal insufflation-exsufflation and manually assisted cough; further research into their effectiveness in different sub groups of people is needed. The use of PCF is a consistent outcome yet would benefit further studies on reliability.

The problem of decreased respiratory muscle strength

Two main therapies were identified to address the problem of respiratory muscle weakness; non invasive ventilation (NIV) and respiratory muscle training. NIV aims to reduce the work of breathing and conserve energy whilst respiratory muscle training aims to strengthen inspiratory and expiratory muscles and improve endurance. Studies of effectiveness of these interventions include a systematic review of eight randomised control trials, five randomised controlled trials, five prospective observational studies, two retrospective observational studies and five experimental studies; see Tables 3 and 4 for details.

Non-invasive ventilation

Ten studies (see Table 3) involved non invasive ventilation as an intervention. The systematic review was specific to ALS. Other studies included 391 people with ALS and 68 mixed population studies. Studies were mainly prospective observational studies (n= 5), with two retrospective studies and two experimental studies. Interventions included Bi level

positive airway pressure (BiPAP), volume cycled NIV and pressure cycled NIV. Outcome measures included FVC, SNIP, MIP, MEP, respiratory muscle endurance and lung compliance.

Table 3

A systematic review (23) identified eight randomised control trials investigating the efficacy of nocturnal mechanical ventilation in relieving hypoventilation related symptoms in patients with neuromuscular and chest wall disorders. Neuromuscular in this review included people with ALS. The primary outcome measure was reversal of daytime hypoventilation symptoms with few studies reporting lung function measurements. The findings of the review suggest benefit of NIV in the short term, but the evidence is weak.

Seven studies, not included in the above review, investigated the effect of NIV on lung function in people with ALS (n= 391). Four studies (n= 282) demonstrated a slower decline in FVC in people tolerating NIV (24-27). NIV intervention was individualised to the patient by mode and length of time of intervention. The evidence is weakened by the fact that Kleopa *et al* (26) and Carratu *et al* (25) are retrospective studies.

Inconclusive evidence exists in relation to other measures of lung function. Aboussouan *et al* (28) found no change in FVC, FEV_1, MIP or MEP; Butz *et al* (29) identified increased oxygenation (SaO_2 and PaO_2) and Lechtzin *et al* (8) showed increased lung compliance following NIV. Two studies including 29 subjects with a range of neurodegenerative conditions identified increased respiratory muscle endurance (30) and improved oxygenation (31) following NIV intervention.

Summary of findings on non-invasive ventilation

The key findings are that NIV may influence lung function in people with ALS/MND and it is recommended to improve quality of life and survival as well as alleviating breathlessness.

The role of NIV in the management of other neurodegenerative conditions needs to be explored.

Respiratory muscle training

Respiratory muscle training techniques using the same principles as those for skeletal muscle training i.e. overload, specificity and reversibility, have been shown to improve respiratory strength and endurance in healthy subjects (32) and in chronic respiratory disease (33). Training may also influence respiratory muscle endurance, dependent upon the training protocol. Outcome measures include maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP) and 12 second maximal voluntary ventilation (12MVV).

Nine studies, including four randomised control studies (see Table 4), assessed the effect of respiratory muscle training in people with neurodegenerative conditions. Two randomised control studies in 61 people with multiple sclerosis (34, 35) and one study including 20 people with Parkinson's disease (36) identified significant increases in MIP following inspiratory muscle training (IMT). The trial by Cheah *et al* (37) only demonstrated trends of increased inspiratory pressure measured by MIP and sniff nasal inspiratory pressure when compared to sham IMT in 19 people with ALS. Studies lasted between 10 and 12 weeks with training ranging from daily to every other day. Although Fry *et al* (34) did not see a change in maximal voluntary ventilation (MVV), Inzelberg *et al* (36) did see a significant increase in inspiratory muscle endurance as measured by the peak pressure obtained on breathing against progressive loads to fatigue.

Table 4

The efficacy of expiratory muscle training is less clear than that of IMT. Two randomised control trials demonstrated significant increases in MEP in 48 people with multiple sclerosis compared to breathing exercises (1) and control group (38). Chiara *et al* (39) also found

significant increases in MEP in 17 people with multiple sclerosis after 8 weeks training. A shorter study by Pitts *et al* (40) of 4 weeks EMT in people with Parkinson's disease showed a significant increase in MEP, but no difference in peak cough flow. The length of training (daily for 3 months (1, 38); daily for 8 weeks (39); 5 days/week for 4 weeks (40)) and different stages of disease (mild (38) mild/moderate (39, 40) and severe (1)) may explain the different results.

In a pilot study by Olgiati *et al* (41), 8 people with multiple sclerosis were assigned either IMT or EMT, dependent upon whether the subjects MIP or MEP was < 70% predicted. Although training was only for 4 weeks, significant increases were observed in MIP, MEP and MVV for the whole group.

Summary of studies on respiratory muscle training

There is some evidence that respiratory muscle training does increase strength and endurance. The majority of studies were carried out on people with multiple sclerosis and therefore results may be specific to this population. Although a number of studies were randomised controlled trials, interventions and outcomes used differed, limiting firm conclusions. Further research is needed to investigate pathophysiological changes occurring in respiratory muscles of people with neurodegenerative conditions and the physiological and clinical effects of respiratory muscle training.

The influence of exercise on respiratory function

Six studies investigated the influence of different types of exercise in people with neurodegenerative conditions (see Table 6). Three studies (n=168 people with multiple sclerosis (42-44)) compared bike training with neurological rehabilitation with only Mostert and Kesselring (42) finding a significant difference in FVC and PEFR in the exercise group. A specific pulmonary rehabilitation program in 9 people with Parkinson's disease (45) and diaphragmatic training in 8 people with ALS (46) did not show any significant changes in respiratory function. In contrast, an intervention of breathing enhanced upper extremity

exercise in 40 people with multiple sclerosis demonstrated a trend of increased FVC and MEP compared to a control group (47). The lack of significant changes in respiratory function may be due to the length of the training programmes which ranged from 3 to 8 weeks.

Further research is needed in terms of the effects of general exercise in people with neurodegenerative conditions and how this is influenced by and influences respiratory function.

Discussion

Summary of evidence

This review selected 35 studies related to physiotherapy based interventions for respiratory function. Interventions were summarised as those aiming to: improve cough effectiveness; mobilise secretions; decrease the work of breathing; increase strength of the respiratory muscles; influence respiratory function through exercise. The evidence selected was weak due to both lack of power and reproducibility of interventions, as highlighted in Table 2. Synthesis of evidence through a meta-analysis was not possible due to heterogeneous populations, interventions and outcome measures; thus a narrative review was undertaken. Cough effectiveness may be improved by using maximal insufflation/exsufflation and manually assisted cough. High frequency chest wall oscillation to mobilise secretions did not influence respiratory function but may reduce breathlessness. The evidence for these positive effects is weak. Non-invasive ventilation to reduce the work of breathing may have an influence on lung function in the short term. Respiratory muscle strength and endurance may be improved using specific training programmes. The evidence relating to exercise as an intervention to improve lung function was inconclusive.

This weak evidence base and anecdotal evidence from discussions with the European Huntington's Disease Network Physiotherapy Working Group (http://www.euro-hd.net/html/network/groups/physio) indicates that further research is needed in people with

neurodegenerative conditions. Knowledge gaps exist in a number of specific areas. Firstly, the mechanisms underlying respiratory problems in people with neurodegenerative conditions such as multiple sclerosis, Parkinson's disease, Huntington's disease and motor neurone disease are unknown. Respiratory function throughout disease progression needs to be explored in order to identify when changes occur and therefore when physiotherapy interventions, both preventative and restorative, should be implemented. The effectiveness of physiotherapy interventions can be explored through studies with bigger numbers, which could be achieved through multi-centre trials, using PCF, MIP and MEP as outcome measures. The over arching aim of further research would be to provide evidence based guidelines for the management of respiratory problems specific to people with neurodegenerative conditions.

Limitations

The review is limited by the number and quality of studies and consequently a meta–analysis was not feasible. Studies had heterogeneous populations, were under powered, often non-randomised and of insufficient number to provide guidelines for management of the different stages of progressive conditions. Interventions and outcome measures were not standardised between studies.

The process of review was limited by having one reviewer rather than two, thus introducing potential bias to the review. This was minimised by using the PICO structure (10) for searching and the CASP appraisal tool (12).

Conclusions

The evidence to support the use of methods to increase cough effectiveness, respiratory muscle strength and endurance in people with neurodegenerative conditions is weak but does indicate a positive effect. The strongest evidence is for the use of non invasive ventilation in people with ALS to alleviate symptoms of chronic hypoventilation. Further research must be focused towards developing guidelines for effective management of

respiratory problems in people with neurodegenerative conditions that take into consideration the pathophysiological similarities and differences in those conditions.

Ethical approval: none required

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Conflict of interest: None declared

Key to abbreviations:

Conditions

ALS	Amyotrophic lateral sclerosis
MND	motor neurone disease
MS	multiple sclerosis
NDC	neurodegenerative conditions
PD	Parkinson's disease
Hc	healthy control

Interventions

BiPAP	bi level positive airway pressure
Br exs	breathing exercises
EMT	Expiratory muscle training
HFCWO	High frequency chest wall oscillation
IMT	Inspiratory muscle training
MAC	Manually assisted cough
MIC	Maximal insufflation capacity
MIE	mechanical insufflation-exsufflation
MHI	manual hyperinflation

NIV	non-invasive ventilation
RMT	respiratory muscle training

Outcomes

12MVV	12 second maximal voluntary ventilation
ABG	Arterial blood gases
FEV_1	Forced expiratory volume in 1 second
FER	Forced expiratory ratio
FVC	Forced vital capacity
MEP	maximal expiratory pressure
MIP	maximal inspiratory pressure
MVV	maximal voluntary ventilation
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
PCF	Peak cough flow
PEFR	peak expiratory flow rate
SaO_2	% saturation of oxygen
SNIP	sniff nasal inspiratory pressure
TLim	respiratory muscle endurance time

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Tables

Table 1 Summary of critical appraisal of all selected studies

	Study design	Focused question	Appropriate design	Population defined	Sample size calculation	Allocation defined	Intervention reproducible	Outcome measures defined	Data analysis defined	Inferential analysis employed	Appropriate interpretation	generalisability	Clinical relevance discussed
Annane et al (24)	EBR	yes	yes	yes	n/a	n/a	n/a	yes	yes	n/a	yes	yes	yes
Aboussouan et al(29)	Obs (P)	yes	yes	yes	no	n/a	no	yes	yes	yes	yes	no	yes
Bach (15)	Exp	yes	yes	yes	no	n/a	no	yes	no	yes	yes	no	yes
Bourke et al (25)	Obs (P)	yes	yes	yes	no	n/a	yes	yes	no	yes	yes	no	yes
Butz et al (30)	Obs (P)	yes	yes	yes	no	n/a	no	yes	yes	yes	yes	no	yes
Carratu et al (26)	Obs (R)	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Chaisson et al (22)	Exp	yes	yes	yes	no	yes	no	yes	yes	yes	yes	no	yes
Chatwin et al (16)	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Cheah et al (38)	RCT	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	yes
Chiara et al (40)	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Fry et al (35)	RCT	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	yes

Gosselink et al (1)	RCT	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Goldstein et al (31)	Exp	yes	yes	yes	no	n/a	no	yes	yes	yes	yes	no	yes
Inzelberg et al (37)	Exp	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	yes
Jackson et al (23)	Obs (R)	yes	no	yes	no	n/a	no	yes	yes	yes	yes	no	yes
Kleopa et al (27)	Obs (R)	yes	yes	yes	no	n/a	no	yes	yes	yes	yes	no	yes
	Study design	Focused question	Appropriate design	Population defined	Sample size calculation	Allocation defined	Intervention reproducible	Outcome measures defined	Data analysis defined	Inferential analysis employed	Appropriate interpretation	generalisability	Clinical relevance discussed
Klefbeck & Hamrah 36)	RCT	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	yes
Koseoglu et al (46)	Exp	yes	yes	yes	no	n/a	no	yes	yes	yes	yes	no	yes
Lange et al (21)	RCT	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes
Lechtzin et al (8)	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
LoCoco et al(28)	Obs (P)	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Mostert & Kesselring (43)	Exp	yes	yes	yes	no	yes	no	yes	yes	yes	yes	no	yes
Mustfa et al	Exp	no	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes

(17)													
Mutluay et al (48)	RCT	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes
Nardin et al (47)	Exp	yes	yes	yes	yes	n/a	yes	yes	yes	yes	yes	no	yes
Nauffal et al (32)	Obs (P)	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Olgiati et al (42)	Exp	yes	yes	yes	no	n/a	no	yes	no	yes	yes	no	yes
Pitts et al (41)	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Rampello et al (45)	Exp	yes	yes	yes	no	yes	no	yes	yes	yes	yes	no	yes
Rasova et al (44)	Exp	no	yes	yes	no	yes	no	yes	yes	yes	yes	no	yes
Sancho et al (18)	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Smeltzer et al (39)	RCT	yes	yes	yes	no	yes	no	yes	yes	yes	yes	no	yes
Suleman et al (20)	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Trebbia et al (19)	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Winck et al (14)	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes

Key

EBR Evidence based review

Exp Experimental

Obs (P)	Observational (prospective) study
Obs (R)	Observational (retrospective) study
RCT	Randomised controlled trial

Table 2 Detail of studies related to retained secretions

Study	Population	Intervention and method	Relevant Outcome measure	Key significant findings
Bach 1993 (15)	21 NDC	MIC, MIC & MAC, MIE Single group; repeated measures from interventions. MIE = several 5 cycle applications at comfortable pressures	PCF	MIE better than MIC &MAC which was better than MIC at ↑ PCF
Chatwin et al 2003 (16)	21 adult and child NDC	Unassisted cough, physiotherapy assisted cough, non-invasive ventilator assisted cough, exsufflation assisted cough, insufflations/exsufflation assisted cough Single group; repeated measures from each intervention.	PCF	Exsufflation assisted cough and insufflation/exsufflation cough better than unassisted cough
Chaisson et al 2006 (22)	9 ALS	HFCWO, standard treatment 2 groups: group 1 - standard care plus	FVC	No difference in rate of decline in FVC between HFCWO and standard treatment

		HFCWO applied for 15min, twice daily; group 2 - standard care. Both groups received instruction on cough augmentation manoeuvres		
Jackson et al 2006 (23)	18 ALS	HFCWO Retrospective study, HFCWO applied twice daily for 10-20 minutes or more frequently if needed. Frequency = 10-14 Hz, pressures 30 – 40 cmH_2O	PCF	No significant changes
Lange et al 2006 (21)	46 ALS	HFCWO, no treatment RCT. HFCWO – twice daily for 10-15 minutes, for 12 weeks. Frequency = 10-12 Hz, pressures 1-4 (linear scale no units). Control group – no treatment.	PEFR, dyspnoea, FVC	↓dyspnoea; FVC decreased in control group and not the HFCWO group.
Mustfa et al 2003 (17)	47 ALS	Cough, MAC, maximal exsufflation, maximal insufflation, MIE Single group, repeated measures from each	PCF	Exsufflation and MIE ↑ PCF

		intervention.		
Sancho et al 2004 (18)	26 ALS	MAC, MIE & MAC Single group, repeated measures from each intervention. MIE = pressure 40 to -40 cmH_2O, I/E ratio 2:3 with 1 sec pause.	PCF	MIE can increase PCF in stable patients with ALS with 4L/s < PCF_{MIC} > 2.7L/s
Suleman et al 2004 (20)	10 MND	Mechanical glottis, cough Single group, repeated measures from each intervention	PEFR	↑ PEFR with mechanical glottis. PEFR with mechanical glottis > PEFR with cough
Trebbia et al 2005 (19)	10 NDC	MHI, MAC, MI & MAC Single group, repeated measures from each intervention.	PCF	PCF higher during MI & MAC than MI and MAC alone
Winck et al 2004 (14)	13 ALS 7 NDC	MIE Single group, measures taken before and after MIE. MIE = 6 I-E cycles at each of 15 to -15 cm H_2O, 30 to -30 cm H_2O, 40 to -40 cm H_2O; I/E ratio 3:4 with 4 sec pause between each cycle.	PCF, SaO_2, dyspnoea	↑ PCF, SaO_2 ↓dyspnoea

Table 3 Detail of studies related to NIV intervention for decreased respiratory muscle strength

Study	Population	Intervention and method	Relevant Outcome measure	Key significant findings
Annane et al 2009 (24)	Neuromuscular or chest wall disorders	Nocturnal mechanical ventilation Cochrane review	FVC, SNIP, SaO_2	Current evidence weak but consistent that nocturnal mechanical ventilation alleviates chronic hypoventilation in the short term.
Aboussouan et al 2001 (29)	60 ALS	NIV Single group, repeated measures over time. NIV = volume controlled or BiPAP; pressures – for patient comfort; for as long as tolerated during night and as necessary daytime.	FVC, FEV_1, MIP, MEP	No significant change in outcomes over time
Bourke et al	17 ALS	BiPAP	FVC	Rate of decline in

2003 (25)		Single group, repeated measures over time. BiPAP = pressures – dependant on arterial blood gases, oxygen saturation and compliance; timing adjusted for patient comfort.		FVC slower post treatment
Butz et al 2003 (30)	30 ALS	NIV Single group, repeated measures over time. NIV = pressure cycled; pressures 8-22 millibars dependent upon arterial blood gases, oxygen saturation and relief of symptoms	FVC, SaO_2, PaO_2, $PaCO_2$	SaO_2 and PaO_2 increased over time
Carratu et al 2009 (26)	72 ALS	NIV Retrospective comparing 3 groups according to FVC and NIV use. NIV = volume controlled or BiPAP; pressures – 8 cmH_2O IPAP, 3 cmH_2O EPAP;	FVC, FEV_1, PaO_2, $PaCO_2$	FVC decline slower in survivors who tolerated NIPPV

		volume/pressure dependent upon chest rise, leaks and comfort; used nightly as tolerated and as necessary daytime.		
Goldstein et al 1991 (31)	6 inc 2 NDC	NIV Single group, repeated measures over time. NIPPV = volume cycled	Tlim	Tlim ↑ at 3 months post intervention
Kleopa et al 1999 (27)	122 ALS	BiPAP Retrospective comparing 3 groups – those who tolerated BiPAP for > 4 hours, those that tolerated < 4 hours and those who refused.	%FVC predicted	Decline of %FVC slower in those who could tolerate NIPPV
Lechtzin et al 2006 (8)	19 ALS, 4 Hc	BiPAP 2 groups, measured before and after BiPAP. BiPAP = 5 minutes; pressure dependent upon lung compliance	FEV_1, FVC, FER, MIP, MEP, static lung compliance	Lung compliance ↑with BiPaP in ALS group, no change in control group

LoCoco et al 2006 (28)	71 ALS	BiPAP Single group, repeated measures over time. BiPAP = pressures adjusted to patient comfort, leaks and efficiency of ventilation; for as long as tolerated nightly and as necessary daytime	FVC	Decline of FVC slower in those who could tolerate NIPPV
Nauffal et al 2002 (32)	62 inc 27 NDC	BiPAP Single group, repeated measures over time. BiPAP nightly; pressures dependent on arterial blood gases.	FEV_1, FVC, FER, MIP, MEP, ABG	SaO_2, ↑ after 3 months FEV_1, FVC ↓ after 12 months

Table 4 Detail of studies related to respiratory muscle training intervention for decreased respiratory muscle strength

Study	Population	Intervention	Relevant Outcome measure	Key significant findings
Cheah et al 2009 (38)	19 ALS	IMT group vs. Sham group IMT 10 minutes, 3 times daily, 12 weeks. Resistance increased weekly from 15 to 60% SNIP, then sustained at 60% SNIP. Sham device had no resistance.	FVC, MIP, SNIP, MEP	FVC, MIP, SNIP ↑ trend
Chiara et al 2006 (40)	17 MS, 14 Hc	EMT Repeated measures pre EMT , post EMT and 4 weeks after no training. EMT 4 sets of 6 repetitions, 5 days a week, 8 weeks. Resistance increased weekly from 40 to 80% MEP then sustained at 80% MEP	FVC, FEV_1, MEP, PEFR	MEP, PEF ↑after 8 weeks training. No difference between MS and hc
Fry et al	46 MS	Home IMT group vs.	MIP, MEP,	MIP ↑

2007 (35)		Control group IMT 3 sets of 15 repetitions, daily for 10 weeks. Resistance increased from 30% MIP according to Borg RPE and symptoms. Control: no intervention.	MVV	
Gosselink et al 2000 (1)	28 MS	EMT group vs. br exs group EMT 3 sets of 15 repetitions, twice daily for 3 months. Resistance was 60% MEP. Br exs to enhance maximal inspirations	FVC, MIP, MEP	MIP ↑after 3 months training, no difference between EMT and br exs. MEP ↑after 3 months and significant compared to br exs
Inzelberg et al 2005 (37)	20 PD	IMT group vs. Control group IMT 30mins, 6 days/week, 12 weeks. Resistance increased from 15 to 60% MIP and sustained at 60% MIP. Control frequency as IMT. Resistance 7 cmH_2O	FVC, MIP, Peak max endurance	MIP and endurance ↑; no change in FVC; no change in control group.

Klefbeck and Hamrah 2003 (36)	15 MS	IMT group vs. Control group IMT 3 sets of 10 repetitions, twice every other day, 10 weeks. Resistance 40-60% MIP, dependent upon Borg RPE < 17 Control deep breathing exercises as part of physiotherapy treatment.	FVC, FEV_1, MIP, MEP, PEFR	MIP and MEP ↑ from baseline. MIP significantly ↑ compared to control.
Olgiati et al 1988 (42)	8 MS	IMT /EMT dependent upon % MIP/MEP Training 6-10 minutes, twice/day, 5 days/ week for 4 ±1 week. Resistance dependent upon %MIP/MEP and progressively increased.	MIP, MEP, MVV	MIP, MEP, MVV ↑
Pitts et al 2009 (41)	10 PD	EMT Repeated measures over time Training 5 sets of 5 breaths, once/day, 5 days week for 4 weeks. Resistance 75% of MEP	MEP, PCF	MEP ↑
Smeltzer	20 MS	EMT group vs. Control	MIP, MEP	MEP↑

et al 1996 (39)		group EMT 3 sets of 15 repetitions, twice daily for 3 months. Resistance based on MEP and increased based on ability to perform exercises. Control frequency as EMT, with IMT at resistances too low to affect inspiratory muscle strength.		

Table 5 Detail on studies based on exercise and its influence on respiratory function

Study	Population	Intervention	Relevant Outcome measure	Key significant findings
Koseoglu et al 1997 (46)	9 PD	Pulmonary rehabilitation Single group compared before and after intervention. Pulmonary Rehabilitation 60 minutes, 3 days/week for 5 weeks.	FVC, FEV_1, PEFR, MVV	No significant changes
Mostert and Kasserling 2002 (43)	37 MS, 26 Hc	MS exercise training (bike)group vs. MS control group vs Hc group vs healthy exercise training group Training 30 minutes, 5 times/week for 3-4 weeks, individualised intensity. MS Control group – normal physiotherapy Hc group – no physical exercise that could improve aerobic fitness	FVC, FEV_1, FER, PEFR, MVV, aerobic capacity	FVC, PEFR ↑ in exercise group; no change in aerobic capacity
Mutluay et al 2007 (48)	62 MS	Breathing enhanced upper extremity exercises group vs. Control group	FVC, FEV_1, FER, MIP, MEP	FEV_1, FER ↑ in compared to control.

		Breathing exercises programme 30 minutes, once/day for 6 weeks		MEP ↑trend compared to control
Nardin et al 2008 (47)	8 ALS	Diaphragmatic training Single group measured before and after intervention. Training 5 sets of 10 minutes daily for 12 weeks	FVC, hypercapnic ventilatory response	No change
Rampello et al 2007 (45)	19 MS	Aerobic training (cycle ergometer) vs. neurological rehabilitation Randomised cross over study. Training 55 minutes, 3 times/week for 8 weeks. Intensity dependent on work rate and increased to 80% maximum work rate Rehabilitation 60 minutes, 3 times/week for 8 weeks.	FVC, FEV_1, MIP, MEP	No difference in lung function
Rasova et al 2006 (44)	112 MS	Neurophysiological physiotherapy vs. aerobic bike training vs. mixed vs. Control Physiotherapy 1 hour,	FVC, FEV_1, PEFR	PEFR ↑ in intervention groups, no difference between groups

		twice/week for 2 months Bike training twice/week, intensity 60% maximal oxygen uptake, time dependent on disability score range 10-30 minutes Mixed training 1 hour twice/week physiotherapy and bike training as above. Control – no intervention.		