

REVIEW

A systematic review and meta-analysis of the effects of respiratory muscle training on pulmonary function in tetraplegia

J Tamplin¹ and DJ Berlowitz^{1,2}**Study design:** Systematic review**Objectives:** To determine the effect of respiratory muscle training (RMT) on pulmonary function in tetraplegia.**Methods:** A comprehensive search of the research literature included MEDLINE, EMBASE, CINAHL, ISI Web of Science, PubMed, the relevant Cochrane and clinical trials registers and hand-searching the reference lists of appropriate papers. There was no language restriction. All randomised controlled trials that involved RMT vs control were considered for inclusion. Two reviewers independently selected articles for inclusion, evaluated the methodological quality and extracted data. Additional information was sought from the authors when necessary.**Results:** Eleven studies (212 participants) were included. A significant benefit of RMT was revealed for five outcomes: vital capacity (mean difference (95% confidence interval))=0.41(0.17–0.64) l, maximal inspiratory pressure=10.66(3.59, 17.72) cmH₂O, maximal expiratory pressure=10.31(2.80–17.82) cmH₂O, maximum voluntary ventilation=17.51(5.20, 29.81) l min⁻¹ and inspiratory capacity=0.35(0.05, 0.65) l. No effect was found for total lung capacity, peak expiratory flow rate, functional residual capacity, residual volume, expiratory reserve volume or forced expiratory volume in 1 second.**Conclusion:** RMT increases respiratory strength, function and endurance during the period of training. Further research is needed to determine optimum dosages and duration of effect. This article is based in part on a Cochrane review published in the Cochrane Database of Systematic Reviews (CDSR) 2013, DOI:10.1002/14651858.CD008507.pub2. Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the CDSR should be consulted for the most recent version of the review. *Spinal Cord* (2014) **52**, 175–180; doi:10.1038/sc.2013.162; published online 14 January 2014**Keywords:** spinal cord injury; tetraplegia; respiratory function; respiratory muscle training; systematic review

INTRODUCTION

Respiratory dysfunction remains a significant cause of illness and death for people with tetraplegia.¹ Recent research indicates that in the 5 years following acute spinal cord injury (SCI), pulmonary function declines at a rate that exceeds the normal age-related decline.² Injury to the spinal cord impairs neuronal control of the respiratory muscles, leading to high incidence of respiratory complications, in particular pulmonary secretion retention, atelectasis, pneumonia and respiratory failure.³ Both inspiration and expiration are compromised in tetraplegia. Impaired inspiratory muscle function prevents deep breaths, reduces vital capacity and may lead to atelectasis and/or dyspnoea with exertion.³ Impaired expiratory muscle function impairs cough and secretion clearance and increases the incidence of lower respiratory tract infections.⁴ As such, respiratory dysfunction secondary to muscle weakness considerably affects the health and health-related quality of life for people with SCI.

The respiratory muscles can be trained in a similar way to the limb muscles by using tasks that increase the load on the muscles.⁵ Various types of respiratory muscle training (RMT) to improve respiratory strength and endurance have been described for people with tetraplegia. These include the use of both resistive and threshold trainers, which typically involve a one-way valve system that

selectively trains either the inspiratory or the expiratory muscles. Normocapnic hyperpnoea^{6,7} and singing training⁸ have also been reported as effective forms of RMT that simultaneously involve the inspiratory and expiratory muscles. Typical training sessions consist of a certain number of exercise repetitions or a particular length of time spent exercising.

Previous attempts at systematically reviewing the research to evaluate the effect of RMT in patients with SCI^{9–11} have reported that heterogeneity, in terms of research design, participant characteristics, training techniques used and outcomes measured, has prohibited meta-analysis. We recently published a Cochrane review (including meta-analysis) of RMT in cervical SCI.¹² As per the focus of the Cochrane collaborative, the outcomes in that review were selected from a consumer poll of outcomes that were considered meaningful from the perspective of this population. These 'Cochrane' outcomes were the frequency of respiratory complications, dyspnoea, vital capacity (VC), maximal inspiratory and expiratory pressures (MIP and MEP), forced expiratory volume in one second (FEV₁) and quality of life. This current systematic review and meta-analysis complements those results but specifically addresses the full range of pulmonary function outcomes that have been reported in the literature.

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MATERIALS AND METHODS

A comprehensive search of the research literature before March 2013 included electronic databases (MEDLINE, EMBASE, CINAHL, ISI Web of Science, PubMed), the relevant Cochrane and clinical trials registers and hand-searching of the reference lists of relevant papers and literature reviews. We used the following keywords in the search: (1) SCI, tetraplegia and synonyms, and (2) RMT and synonyms (the full Medline search strategy is presented in Appendix 1). There was no language restriction. Inclusion criteria were as follows: (1) participants with any level of acquired cervical SCI, both acute and chronic; (2) an intervention described as RMT; (3) randomised controlled trial design (that is, a randomised comparison group using an alternative intervention, placebo, usual care or no intervention). Studies of RMT for people with inherited or congenital neuromuscular disorders (such as muscular dystrophies, congenital and acquired myopathies and spinal muscular atrophy) or respiratory disorders not caused by spinal injury (such as COPD and asthma) were excluded.

Static lung and spirometric measures analysed for this review included total lung capacity (TLC), forced vital capacity (FVC), VC, functional residual capacity (FRC), residual volume (RV), expiratory reserve volume (ERV), FEV₁, FEV₁ as a proportion of FVC (FEV₁/FVC), inspiratory capacity (IC) and peak expiratory flow rate (PEFR). Measures of respiratory muscle strength (MIP and MEP) and of the maximum voluntary ventilation (MVV) were also extracted.

Two reviewers independently selected articles for inclusion, evaluated the methodological quality and extracted data. Disagreement between reviewers was resolved through discussion, and additional information was sought from trial authors when necessary. Revman (Version 5.2) software was used to analyse the results. Results are presented as mean differences (using post-test scores) and 95% confidence intervals.

The papers were screened and the raw data extracted at the same time as the Cochrane paper. We explicitly performed the Cochrane analyses first, addressing only the selected variables and hypotheses that were to be included in the Cochrane review. Following the acceptance of the Cochrane paper, we performed the analysis on the 'extended' outcomes as described in this paper and reached the conclusions as described.

RESULTS

A total of 843 citations were identified from the sources above. After removing duplicates and animal studies, the titles and abstracts of 747 citations were reviewed and the full text for 40 publications retrieved. Of these, 28 were excluded on the basis of design (not randomised, $n = 26$), ineligible populations ($n = 3$) or ineligible intervention (not RMT, $n = 4$). A full list of these excluded studies can be found in the Cochrane review.¹²

Eleven studies (12 publications) with a total of 212 participants met all the inclusion criteria and were included in the review (Table 1). One study¹³ had a cross-over design, and in the remaining 10 studies there were four comparisons between RMT and an alternative intervention,^{6,8,14,15} and seven comparisons against a control condition (three vs a sham treatment^{6,7,16} and four vs 'usual care').^{17–20} Sample sizes for the included studies ranged from 9 to 40 participants, and injury level ranged from C4 to C8. Some studies included participants with thoracic-level injuries^{7,16} and non-traumatic SCI.^{15,19} Testing position was not consistent across the studies. Six studies tested participants in a seated position,^{6–8,15,16,19} whereas two studies used a supine testing position.^{14,18} Two studies tested in both positions^{13,17} and one study did not report the testing position.²⁰ Wearing an abdominal binder during respiratory function testing has been reported to deliver better results for people with tetraplegia, in a similar manner to testing in the supine position.²¹ Only two of the six studies that used an upright sitting position for testing stated that an abdominal binder was not used.^{6,8} A minority of studies demonstrated strong methodological rigor, with few adequately reporting allocation concealment^{7,8} and blinding

procedures.^{6–8,16} In addition, six studies failed to report outcome data for participants who did not complete the trial.^{6,14–16,18,19}

Two of the included studies^{6,15} compared two different RMT interventions with a control condition. To facilitate clear comparison of interventions in the meta-analysis, the Mueller⁶ inspiratory resistance training comparison (vs control) is referred to as Mueller 2013 (A) and the isocapnic hyperpnoea comparison as Mueller 2013 (B). Similarly, the Litchke¹⁵ flow resistance training comparison is termed Litchke 2010 (A) and the pressure threshold resistance training as Litchke 2010 (B). Eight studies used resistive muscle training devices targeting either inspiratory ($n = 5$)^{6,13,14,18,20} or expiratory ($n = 3$)^{13,16,17} muscle resistance. Five studies simultaneously targeted both inspiratory and expiratory muscle function.^{6–8,15,19} The different interventions ranged in intensity from 10 to 60 min per day, 3 to 7 days per week, and total length of training ranged from 4 to 12 weeks (mean 8 weeks).

Two studies^{13,20} presented data as percentages of predicted normal values rather than raw scores, and thus these data could not be pooled with the other studies for meta-analysis. As there were no common outcomes between these two studies, a comparison of the percentage of predicted scores was not possible. We contacted the authors of these studies, but were not able to obtain any raw data. The majority of included studies did not report change score standard deviations. Thus, we conducted the meta-analysis using mean post-test scores, assuming that any baseline differences between groups would be accounted for through random group allocation. Table 2 presents a summary of the results of the meta-analysis for the pulmonary function variables.

Analyses revealed that RMT statistically significantly improved MIP (mean difference (95% confidence interval)) = 10.66 (3.59, 17.72) cmH₂O, MEP = 10.31 (2.80, 17.82) cmH₂O, MVV = 17.51 (5.20, 29.81) l min⁻¹ (Figure 1) and IC 0.35 (0.05, 0.65) l (Figure 2). No significant effect was found for FEV₁, TLC, FRC, RV, ERV, PEFR rate or FEV₁/FVC. Two included studies reported the VC only,^{6,17} three reported only the FVC^{7,14,16} and two reported both the slow and forced vital capacity.^{8,18} Where both the FVC and VC were reported in the same papers, only the VC was included in the analyses. RMT increased the VC by 0.40 l (0.12, 0.69) and the FVC by 0.41 l (–0.02, 0.84), giving a combined estimate of benefit of 0.41 l (0.17, 0.64) (Figure 3).

DISCUSSION

This systematic review and meta-analysis focused on the effect of RMT on the full range of pulmonary function measured in tetraplegia. Despite the relatively small number of studies and participants, RMT appears to be particularly effective at increasing vital capacity, inspiratory volumes and strength.

The vital capacity, whether measured as the FVC or the (slow) VC, is a key clinical marker of respiratory health in tetraplegia. In acute injury, a VC below 10 ml per kilogram of body weight predicts the need for intubation,²² and the VC influences both the likelihood of tracheostomy and of weaning success.²³ Similarly, in those with chronic SCI, a lower VC is predictive of pulmonary infection^{24,25} and mortality risk.²⁶ Separate analyses found a statistically significant benefit on VC for IMT but not on FVC; however, the mean differences for the two comparisons were within 10 ml. As illustrated in Figure 3, when the FVC and (slow) VC data were combined, the magnitude of the mean benefit was essentially unchanged and the precision of the estimate increased. Significant airflow obstruction in the participants from the included studies would reduce the FVC relative to the (slow) VC, but examination of the baseline demographic characteristics from the original papers

Table 1 Included studies: RCTs investigating respiratory muscle training in cervical spinal cord injury

Author ^{ref.}	Participants	Methods	Reported outcomes
Derrickson <i>et al.</i> ^{14a}	N = 11 C4–C7 complete Age: 23–34	Treatment: Resistive IMT vs breathing with abdominal weights. Dosage: 2 × 15 min per day, 5 days per week × 7 weeks	Significant improvements for both groups in FVC, MVV, PEFR and MIP. No significant differences between treatment groups for any of the improvements in pulmonary variables; however, mean changes tended to be larger for the IMT group.
Gounden ^{17b}	N = 40 C5–C8 Age: 16–45	Treatment: Progressive resistive EMT vs no training. Dosage: 30 min per day, 5 days per week × 8 weeks	Significant improvements in VC and MEP for the intervention group only.
Liaw <i>et al.</i> ^{18a}	N = 20 C4–C7 Age: 19–48	Treatment: Target resistive IMT vs usual care. Dosage: 15–20 min twice daily × 6 weeks	Greater improvement in VC and TLC for IMT group than control. MIP improved in both groups - could be due to natural recovery post SCI, learning to do the manoeuvre and/or insufficient length of training.
Litchke <i>et al.</i> ^{19c}	N = 9 C5–T12 Age: 21–49	Treatment: Respiratory resistance Training (RRT) vs usual care. Dosage: 10 reps 2–3 times daily × 10 weeks	Increase in MIP significantly greater for the RRT group than control. Nonsignificant increase in MVV for the intervention group vs decrease for the control group.
Litchke <i>et al.</i> ^{15c}	N = 16 C5–C7 Age: 18–50	Treatments: Concurrent flow resistance vs. concurrent pressure threshold resistance vs usual care. Dosage: 10 reps twice daily × 9 weeks	Increase in MVV significantly greater for the CFR group than CPTR. No significant differences between groups for MIP, but moderate effect size for MIP increases in CPTR group vs CFR & control.
Loveridge <i>et al.</i> ^{20a}	N = 12 C6–C7 complete Age: 27–47	Treatment: Resistive IMT without target at 85% maximal sustainable mouth pressure vs usual care. Dosage: 15 min twice daily 5 days per week × 8 weeks	MIP and maximal sustainable mouth pressure increased in both IMT and control with no significant difference between groups.
Mueller <i>et al.</i> ^{6c}	N = 24 C5–C8 Age: 22–58	Treatment: Isocapnic hyperpnoea training vs inspiratory resistance training (irt) vs incentive spirometry (placebo). Dosage: 10 min daily 4 days per week × 8 weeks	Significant effect of IRT vs placebo and vs isocapnic hyperpnoea for inspiratory muscle strength. High effect size for IRT vs isocapnic hyperpnoea for PEFR. High effect sizes for IRT vs placebo for subjective ability 'to blow one's nose' and the physical component of quality of life. High effect sizes for breathlessness during exercise for isocapnic hyperpnoea compared with placebo.
Roth <i>et al.</i> ^{16b}	N = 29 C4–C8 Age: 16–60	Treatment: Expiratory resistance training vs sham. Dosage: 10 reps twice daily 5 days per week × 6 weeks	Significant improvements in MIP & MEP for the intervention group vs control. FVC, FEV ₁ and ERV improved in both groups
Tamplin <i>et al.</i> ^{8c}	N = 24 C4–T1 Age: 27–70	Treatment: Therapeutic singing training vs. music appreciation. Dosage: 1 hour daily 3 days per week × 12 weeks	Nonsignificant trends towards improvement in respiratory function following singing training - particularly respiratory pressures. Significant increases in projected speech intensity and maximum phonation length for the intervention group vs control. Significant improvements in mood for both groups.
Van Houtte <i>et al.</i> ^{7c}	N = 14 C4–T10 Age: 17–66	Treatment: Normocapnic hyperpnoea training vs. sham Dosage: 30 min daily 4 days per week × 8 weeks	Significant improvements in FVC, MVV, MIP and MEP for the intervention group. Improvement trends maintained at the 16-week follow-up for FVC & MVV. Significant between-group differences in MVV after 8 weeks of training and trends towards difference for FVC and MIP in favour of the training group. Improvement on index of pulmonary dysfunction and decreased number of respiratory complications post training.
Zupan <i>et al.</i> ¹³	N = 13 C4–C7 Age: 17–46	Treatment: Target resistive IMT vs maximal expiration exercises with electronic stimulation of abdominal muscles vs for usual care Dosage: 20–30 min twice daily 6 days per week × 4 weeks	Significant increase in FVC and FEV ₁ after IMT. No significant changes when sitting post EMT, but when supine FVC and FEV ₁ increased. No improvement in FVC or FEV ₁ for control group and greater increase for IMT vs EMT.

^aInspiratory muscle training.^bExpiratory muscle training.^cBoth inspiratory and expiratory muscle training.

provides no evidence of airflow obstruction. This observation, coupled with the nearly identical estimate of benefit for the (slow) VC and the FVC, suggests that regardless of the method by which the

effect of RMT on vital capacity is measured, the benefit is real. Recently, Postma *et al.*² have shown that during the first five years after injury a lower MIP and physical fitness and a higher body mass

index are associated with increased pulmonary function decline, as measured by FVC. The current results demonstrate that the vital capacity can be increased with training, and future longitudinal studies should examine whether regular RMT can ameliorate the detrimental effects of ageing with SCI on pulmonary function.

The improvements in MIP, MEP, MVV, VC and IC following RMT that were revealed by the meta-analyses allow us to speculate around causation and mechanisms. The MIP and IC have been directly correlated in previous cross-sectional cohorts²⁷ and the increases observed in this paper are likely to be directly associated with increased strength in the same muscles. Increases in both MIP and IC would likely also result in a larger measured VC despite no change

in 'expiratory' volumes such as the RV. In people with neuromuscular weakness, MVV can be considered to simultaneously measure respiratory strength, lung capacity and (to a degree) endurance and as such considered as an integrated functional measure of ventilatory capacity. The observed increases in MIP, MEP and VC could thus be considered to have led to the MVV increase. These postulated relationships are obviously associative, but the results of the meta-analysis suggest that RMT overall has proven capacity to improve inspiratory muscle strength and function.

Both the MIP and MEP are very sensitive to the absolute lung volume at which they are measured,²⁸ and this may confound interpretation of the observed results. The meta-analysis did not reveal any systematic effect of RMT on the FRC or RV, and as such it is probable that the MIP was measured at about the same absolute lung volume within subjects in these studies. The MEP, however, may have been affected by the absolute lung volume at which it was measured after training. A higher IC would result in the MEP being measured at a higher absolute lung volume after RMT, and as such lung elastic recoil would contribute to the observed value to a larger degree.²⁷ Further, the absence of any demonstrable increase in 'expiratory' measures (PEFR, FEV₁ or ERV) despite the observed increase in MEP may suggest that the elastic recoil effect could have predominated. Most participants in these studies had tetraplegia and thus absent or diminished abdominal and other active expiratory muscle function that could have been trained by RMT. Previous research has demonstrated that the clavicular head of the pectoralis major muscle can be trained to increase the ERV;^{29,30} however, it is not possible in a systematic review such as this to determine the relative contribution of this particular muscle to the overall results. Invasive, comprehensive measurement of pulmonary mechanics should be considered in future trials of RMT in tetraplegia to understand the relative contribution of lung elastic recoil to any observed improvement in MEP.

The ability to expel air forcefully from the lungs, usually by coughing, is an important determinant of respiratory health and effective pulmonary secretion clearance.³¹ The current meta-analyses

Table 2 Summary of meta-analysis results for all included variables

Outcome	No. of studies	No. of participants	Mean difference (95% confidence interval)	Significance (P)
TLC	4	97	0.22 (-0.17, 0.62)	0.26
FVC only	3	54	0.41 (-0.02, 0.84)	0.06
(slow) VC only	4	108	0.40 (0.12, 0.69)	0.006
Combined FVC and VC	7	162	0.41 (0.17, 0.64)	0.0008
IC	3	64	0.35 (0.05, 0.65)	0.02
FRC	3	73	0.05 (-0.27, 0.36)	0.77
RV	4	97	0.14 (-0.35, 0.63)	0.58
ERV	3	77	0.05 (-0.11, 0.20)	0.55
MVV	5	74	17.51 (5.20, 29.81)	0.005
PEFR	4	79	0.25 (-0.48, 0.98)	0.50
FEV ₁	4	97	0.05 (-0.23, 0.34)	0.70
FEV ₁ /FVC	2	44	0.75 (-4.29, 5.78)	0.77
MIP	8	147	10.66 (3.59, 17.72)	0.003
MEP	6	151	10.31 (2.80, 17.82)	0.007

Abbreviations: ERV, expiratory reserve volume; FEV₁, forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; MEP, Maximal expiratory pressure; MIP, maximal inspiratory pressure; MVV, maximum voluntary ventilation; PEFR, peak expiratory flow rate; RV, residual volume; VC, vital capacity.

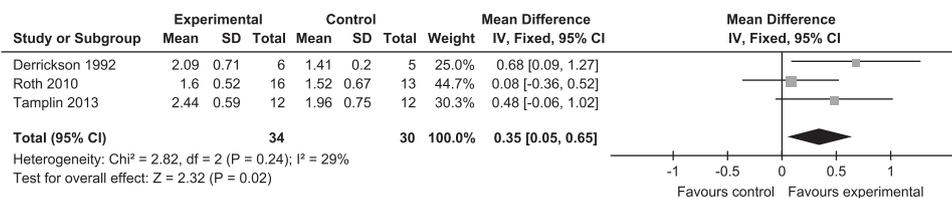
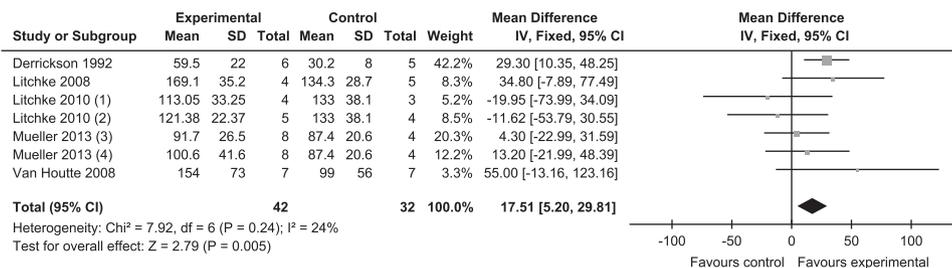


Figure 1 Forest plot of meta-analysis results for inspiratory capacity.



- (1) Litchke B
(2) Litchke A
(3) Mueller B
(4) Mueller A

Figure 2 Forest plot of meta-analysis results for maximum ventilatory ventilation.

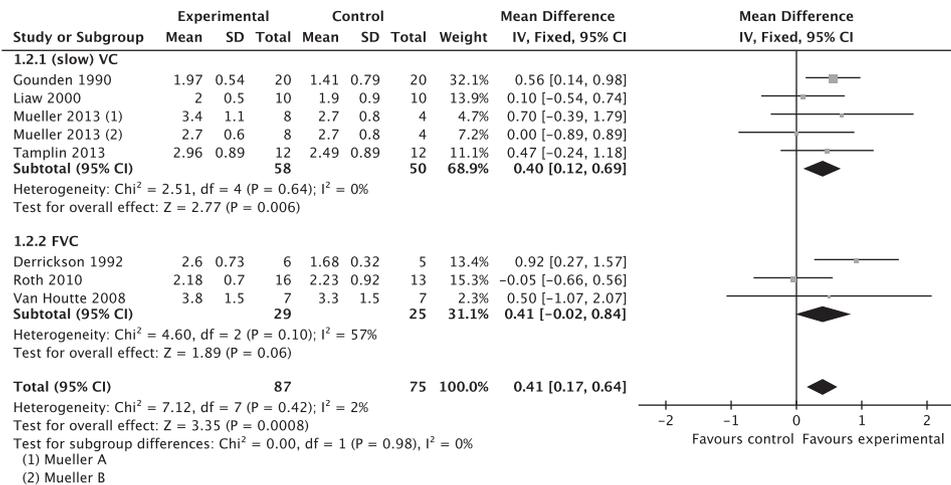


Figure 3 Forest plot of meta-analysis results for vital capacity.

did not demonstrate a significant benefit of RMT on measures associated with an effective cough such as the FEV₁ or the PEF_R. More direct measures of ‘functional’ cough efficacy have been proposed, such as the ‘peak cough flow’; the PEF_R of air expelled during a cough is typically measured using a hand-held ‘asthma’ peak flow meter.³¹ However, there is little standardization in the literature around peak cough flow measurement. It has been variably measured as unassisted, assisted manually or mechanically and with or without a maximal insufflation to total lung capacity.^{31,32} Consideration should be given to the standardization of peak cough flow as an index to enable future comparison and meta-analyses across studies.

An important limitation of this meta-analysis is the inclusion of a few participants with paraplegia in the papers of Van Houtte *et al.*¹¹ and Litchke *et al.*¹⁵ In any meta-analysis, it is always debatable whether it is better to be broadly inclusive in terms of study selection or to be very selective and specific with the selection of studies to be included. In this paper, we chose to be inclusive to examine the overall question as to whether RMT has a role in tetraplegia. As such, four people with paraplegia were included in the Van Houtte and eight in the Litchke data. It was not possible to separate out the data from the individual participants in these papers, but we performed a sensitivity analysis to examine whether removing these studies affected the conclusions of the meta-analyses. Specifically, if we exclude the Litchke *et al.*¹⁵ paper from analyses, the effect estimate is reduced to 15.94 (3.09, 28.79) but remains statistically significant for MVV. Similarly, if we exclude the Van Houtte *et al.*¹¹ study, there is no significant change to the findings (revised estimate of VC effect of 0.40 (0.16, 0.64) and a MVV of 16.24 (3.73, 28.75)).

The results of this meta-analysis indicate that RMT is able to increase the functional capacity of the lungs as measured by MVV, which may affect quality-of-life outcomes for people with tetraplegia. Van Houtte *et al.*¹¹ found that significant improvements in MVV following RMT were coupled with significant improvements in respiratory endurance and health-related quality of life, as measured by the Index of Pulmonary Dysfunction. Litchke *et al.*¹⁵ proposed a similar hypothesis regarding the effect of RMT on overall lung function for wheelchair athletes and the potential subsequent effect on the overall quality of life.

Although 11 studies were included in this review, the meta-analysis relied strongly on the data from five of these.^{6,8,14,16,18} The data from three studies were not able to be included,^{13,17,20} and three papers

reported data for only one^{15,19} or two⁷ of the meta-analysed outcomes. These low numbers of studies and participants may affect the generalizability of these findings. In addition, many of the included studies grouped the participants as ‘complete’ or ‘incomplete’, with little specific data regarding AIS. Future studies should consider using the published, standardized categories of lesion level and severity.³³

CONCLUSION

Despite the relatively small number of studies included, the meta-analysis revealed that RMT increases inspiratory and VC, inspiratory and expiratory pressures and the MVV in people with tetraplegia. Additional research is needed to determine the optimum dosages and duration of effect and to understand whether RMT confers any longer-term functional benefit.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

1. exp spinal cord injuries/
2. exp spinal cord ischemia/
3. exp central cord syndrome/
4. (myelopathy adj3 (traumatic or post-traumatic)).ab,ti.
5. ((spine or spinal) adj3 (fracture\$ or wound\$ or trauma\$ or injur\$ or damag\$)).ab,ti.
6. (spinal cord adj3 (contusion or laceration or transaction or trauma or ischemia)).ab,ti.
7. central cord injury syndrome.ab,ti.
8. central spinal cord syndrome.ab,ti.
9. exp Cervical Vertebrae/in (Injuries)
10. exp spinal cord/
11. SCL.ab,ti.
12. exp paraplegia/
13. exp quadriplegia/
14. (paraplegia* or quadriplegia* or tetraplegia*).ab,ti.
15. or/1–14
16. exp breathing exercises/
17. exp respiratory muscles/
18. exp exercise therapy/
19. (train* or exercis* or endurance or strength* or resistive).ab,ti.
20. 18 or 19
21. 17 and 20
22. normocapnic hyperpnoea training.ab,ti.
23. ((inspiratory or respiratory or breath*) adj5 (endurance or train* or exercis* or resist* or strength*)).ab,ti.
24. RMT.ab,ti.
25. 16 or 21 or 22 or 23 or 24
26. 15 and 25