Journal of Back and Musculoskeletal Rehabilitation 36 (2023) 577–593
DOI 10.3233/BMR-220201
IOS Press

Review Article

Rehabilitation interventions for weaning from mechanical ventilation in patients with spinal cord injury: A systematic review

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Received 26 June 2022
Accepted 4 November 2022

Abstract.
BACKGROUND: Despite the fact that weaning from mechanical ventilation (MV) is one of the main rehabilitation goals in patients with spinal cord injury (SCI), controversies are still open about the optimal rehabilitation approach.
OBJECTIVE: This systematic review aimed at characterizing the rehabilitation interventions currently available to optimize weaning from MV in SCI patients.
METHODS: On April 12[nd], 2022, a systematic literature search was performed in PubMed, Scopus, Web of Science, Cochrane, and PEDro, identifying studies assessing MV patients with SCI undergoing pulmonary rehabilitation. The primary outcomes were weaning duration, MV duration, and weaning success rate. Secondary outcomes were pulmonary function, extubation or decannulation time, length of stay, and safety.
RESULTS: Out of 413 records, 14 studies were included (2 randomized controlled trials, 7 observational studies, and 5 case reports). Most of the studies assessed a comprehensive rehabilitation approach, including high tidal volume ventilation, positioning, mechanical lung recruitment maneuvers, secretion management strategies, respiratory muscle training, and electrical stimulation.
CONCLUSION: Our findings suggested that a comprehensive rehabilitation intervention might have a role in reducing MV duration in patients with SCI. Further studies are needed to better characterize the optimal rehabilitation strategies for enhancing functional recovery of patients with SCI.

Keywords: Mechanical ventilation, spinal cord injury, rehabilitation, weaning, physiotherapy

1. Introduction

Spinal cord injury (SCI) is a detrimental neurological condition leading to impairment in motor, sensory, and visceral controls [1–4]. It has been estimated that SCI prevalence ranges from 13.0 per million to 163.4 per

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ISSN 1053-8127/$35.00

million people with a high heterogeneity among countries [5–7]. In addition, approximately 75% of traumatic SCI involve young adults [5–7]. Therefore, health-care costs are extremely high, while personal and social costs are inestimable.

In this scenario, rehabilitation plays a pivotal role with growing evidence underlining the needing for a comprehensive rehabilitation approach targeting the multilevel physical and psychosocial disabilities of patients with SCI, reducing not only functional impairment and assistance costs but also improving health-related quality of life (HR-QoL) of patients with SCI [8–13].

On the other hand, patients with cervical spinal cord lesions may suffer from a higher level of impairment in different body functions, including cough or breathing due to impaired control of abdominal and/or diaphragm muscles [14]. In particular, it has been reported that more than 90% of traumatic cervical SCIs require intubation, while more than 40% of those patients require chronic mechanical ventilation (MV) [15,16]. Albeit MV is a life-saving intervention in patients with acute respiratory failure, several studies highlighted that prolonged MV crucially affects functional recovery and residual disability, with harmful consequences on length of stay and health-related quality of life (HR-QoL) [17–21]. Moreover, prolonged MV has been associated with a higher risk for infections, ventilator-associated pneumonia (VAP), and atelectasis [22]. As a result, prolonged MV might significantly affect clinical outcomes of patients with SCI, leading to a higher risk of death and lower survival [23–25].

Taken together, these findings highlighted the need for effective rehabilitation programs optimizing weaning from MV in patients with SCI not only to improve disability and promote functional recovery but also to reduce clinical complications and improve life expectancy [7,26].

In recent years, growing evidence highlighted the benefits of respiratory rehabilitation interventions in weaning from MV. More in detail, the recent meta-analysis by Worraphan et al. [27] underlined the effectiveness of inspiratory muscle training (IMT) and early mobilization (EM) in facilitating weaning from MV. However, given the kinesiological differences in respiratory mechanics and the differences in respiratory tract innervation following SCI [28,29], evidence in this specific population is needed to support the effectiveness of rehabilitation in the weaning process of patients with SCI.

Interestingly, the systematic review by Schreiber et al. [30] assessed the patient's characteristics that might affect separation from MV in patients with SCI. However, the authors did not focus on rehabilitation approaches aiming at optimizing the weaning process.

Despite the effects of rehabilitative interventions in weaning from MV have been deeply studied [31–33], there is no clear evidence about specific rehabilitation strategies enhancing the weaning process in patients with SCI. Moreover, to the best of our knowledge, no previous systematic review assessed the effects of different rehabilitation approaches proposed to improve weaning from MV in SCI patients.

Therefore, the aim of this systematic review was to summarize the current evidence about the effects of rehabilitative interventions in reducing MV duration and enhancing the weaning process in patients with SCI.

2. Methods

2.1. Registration

This systematic review has been performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [34]. The international prospective register of systematic reviews (PROSPERO) was preliminary searched for similar review protocols in progress without showing similar reviews. The systematic review was submitted to PROSPERO and accepted on 13th May 2022 (registration number CRD42022329678).

2.2. Search strategy

Five databases (PubMed/Medline, Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and PEDro) were systematically searched simultaneously for studies published until April 12th, 2022. Two investigators independently searched the databases. The full search strategy for each database is reported in Supplementary Table 1.

2.3. Selection criteria

In accordance with the PICO model [35], we considered eligible clinical trials satisfying the following criteria:

- P) Participants: mechanically ventilated patients with spinal cord injury, age $>$ 18 years.
- I) Intervention: we considered all rehabilitation and/or physiotherapy interventions administered as exclusive or integrated interventions.

- C) Comparator: any comparator.
- O) Outcome: the primary outcomes were weaning duration (defined as time between first assessment and the absence of MV for 48 hours), MV duration (defined as time between start of MV and successful weaning), and weaning success rate (express as percentage of patients weaned per whole sample). The secondary outcomes were: i) Pulmonary function; ii) Extubation or decannulation time; iii) Length of stay; iv) Safety.

Only studies published in peer-reviewed International Journal were included. The exclusion criteria were: i) studies involving animals; ii) participants with pregnancy, clinical instability (defined as hemodynamic alterations, respiratory events, abnormal laboratory values, reduced level of consciousness or temperature alterations), or palliation; iii) Masters or doctorate theses, conference proceedings, and literature review; iv) language other than English. No publication date restriction was applied.

After duplication removal, the records were screened by two investigators that independently reviewed titles and abstracts. The articles meeting the enrolment criteria proceeded to the full-text review screening phase. Any disagreements were discussed with a third reviewer to reach consensus.

Lastly, relevant full-text records were assessed in by two independent reviewers; in case of disagreement, it was solved by asking a third reviewer.

2.4. Data extraction and synthesis

All data were extracted by two independent reviewers through Excel. Any disagreement was solved by discussion between the two reviewers or by consulting a third reviewer.

The following data were extracted: 1) Authors; 2) Journal; 3) Publication year; 4) Nationality; 5) Population characteristics; 6) Intervention characteristics; 7) Comparator characteristics; 8) Outcomes; 9) Main findings.

A descriptive approach was used to synthesize both study characteristics and data extracted. The studies were grouped for the syntheses basing on the outcomes assessed. Moreover, subgroup analysis has been performed based on the type of intervention assessed.

2.5. Quality assessment and risk of bias

The quality assessment was performed through Joanna Briggs Institute Critical Appraisal Checklist for Randomized Controlled Trials, JBI Critical Appraisal Checklist for Cohort Studies, JBI Critical Appraisal Checklist for Case Series, or JBI Critical Appraisal Checklist for Case Reports basing on the study design [36]. Two independent reviewers performed independently the quality assessment. A third reviewer was involved in case of disagreement to achieve consensus.

3. Results

3.1. Study characteristics

A total of 407 records were identified from 5 databases assessed, while 6 records were identified from other sources. After duplication removal, 363 studies were assessed for eligibility and screened for title and abstract. As a result, 332 records were excluded, and 31 studies were subsequently screened in full text. Lastly, 14 studies [37–53] were included in the present systematic review. Figure 1 shows further details about the article selection process through the PRISMA flow diagram. Supplementary Table 2 shows the list of the 17 full-text studies assessed for eligibility and excluded, reporting the reasons for exclusion.

As a result, the following studies were included in the present systematic review: Atito-Narh et al. [37], Duarte et al. [38], Fenton et al. [39], Gundogdu et al. [40], Gutierrez et al. [41], Gutierrez et al. [42], Hatton et al. [43], Kim et al. [44], Korupolu et al. [45], McCaughey et al. [46], Peterson et al. [47], Toki et al. [50], Wong et al. [52], and Zhang et al. [53].

The studies included were published between 1999 [47] and 2021 [38,43,45] and were conducted in America (USA $n = 7$ [39,41–43,45,47,52]; Brazil $n = 1$ [38]), Europe (UK $n = 2$ [37,46]), Turkey ($n = 1$ [40]) and Asia (China $n = 1$ [53], Japan $n = 1$ [50]; Korea $n = 1$ [44]). The present review included a total of 525 patients (431 males, 94 females). The sample size ranged from 1, in the Case Report of Zhang et al. [53] to 181 in the cohort study by Hatton et al. [43].

The patients included were characterized by a mean age ranging between 27.24 ± 7.22, as reported in the randomized controlled trial (RCT) of Fenton et al. [39], and 53 (35–70), as reported in the cohort study by Hatton et al. [43], in the comparator group. On the other hand, the case series included patients from 28 ± 14 years old to 68 years old [41].

All studies [37–53] included in this systematic review assessed patients with cervical SCI, while two studies [37,45] included also patients with thoracic SCI.

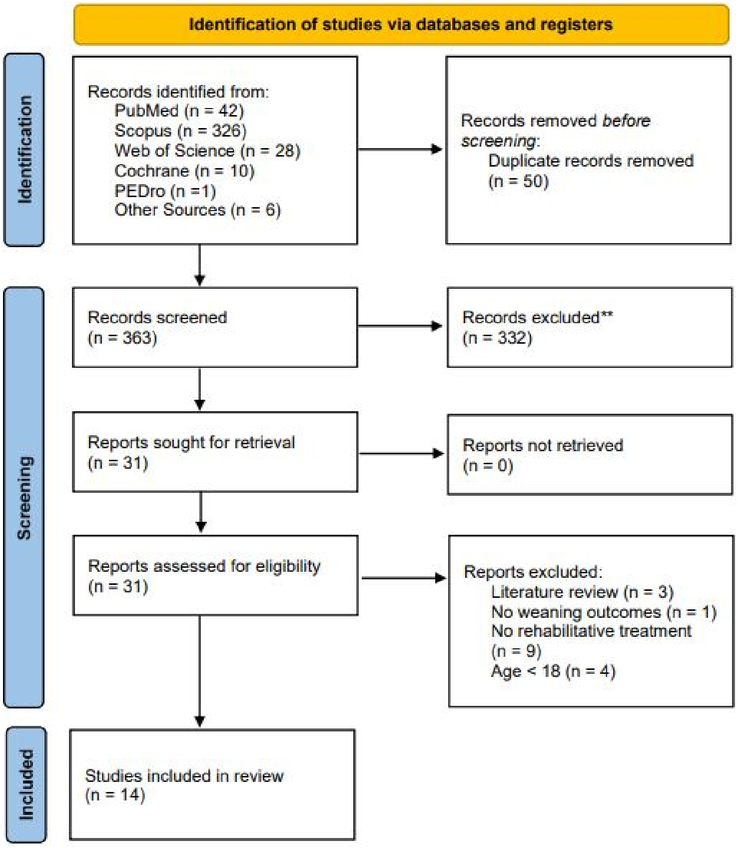

Fig. 1. PRISMA 2020 flow diagram.

Interestingly, most of the studies included [37,38,40, 43–53] assessed acute SCI. In contrast, the RCT of Fenton et al. [39] assessed patients with sub-acute traumatic SCI, while the studies by Gutierrez et al. [41,42] assessed patients with chronic SCI. Asia Impairment Scale (AIS) was used to characterize the functional impairment of SCI in eleven studies [37–40,42,44–46,50, 52,53], while in three studies [41,43,47] the functional impairment was not reported. Table 1 summarizes in detail the sample characteristics of both intervention groups and comparator groups of each study included in the present review.

3.2. Intervention characteristics

Rehabilitation interventions have been classified as changing in MV settings, mobilization/positioning techniques, respiratory muscle training, abdominal or diaphragmatic electrical stimulation, recruitment manoeuvrers (manual hyperinflation or intermitted positive-pressure breathing – IPPB), and secretion management (clearance of airway, swallowing therapy, tracheal suctioning).

- *Changing in MV settings*: Five studies [39,43,45, 47,52] assessed the effects of high Vt mechanical ventilation. More in detail, the RCT of Fenton et al. [39] assessed the effects of high Vt at 20 ml kg^{-1} IBW. In contrast, Hatton et al. [43] assessed high-Vt $>$ 10 cc/kg PBW (mean: 10.8 [10.2–11.3 IQR] cc/kg PBW), Korupolu et al. [45] assessed high-Vt at 15–20 ml/kg PBW, Peterson et al. [47] assessed high-Vt at mean 25.3 ml/kg (range = 20.3 $\pm$ 32.2 ml/kg), Wong et al. [52] assessed high-Vt at 12–15 ml/kg IBW.
- *Mobilization/positioning*: Two studies [37,42] assessed mobilization/positioning as a potential treatment for improving weaning of SCI patients. More in detail, the effects of Trendelenburg chest optimization positioning were assessed in the RCT by Gutierrez et al. [42]. Each positioning session was maintained for about 30 minutes. In contrast, Atito-Narh et al. [37] assessed the effects of different positioning strategies in their treatment protocol. More in detail, the positioning protocol

Table 1
Main characteristics of the studies included

Authors journal year	Nationality	Study design	Participants: Sample size	Age (years)	Male/Female	BMI (kg/m2)	Neurological lesion level (Cervical, Thoracic, Lumbar)	AIS	Chronic/ Acute	Complete/ Incomplete	Intervention	Comparator	Protocol duration	Outcomes	Main findings
Fenton et al. 2016 *Spinal Cord.*	USA	RCT	$N = 33$ IG: 16 CG: 17	IG: 39.31 $\pm$ 12.52 CG: 27.24 $\pm$ 7.22	IG: 14 M/2 F CG: 11 M/6 F	NR	Cervical IG: C1-3: 4 C4: 6 C5: 5 C6: 1 CG: C1-3: 2 C4: 8 C5: 6 C6: 1	AIS A-B-C AIS A: NR AIS B: NR AIS C: NR	Acute	NR	High-Vt 20 ml kg^{-1} IBW	Standard-Vt 10 ml kg^{-1} IBW	Weaning period	* Weaning duration * Pulmonary function * Safety	This study reports about 33 SCI patients on MV admitted to ICU (mean age IG: 39.31 $\pm$ 12.52, CG: 27.24 $\pm$ 7.22; IG: 14 M/2 F, CG: 11 M/6 F). IG underwent to High-Vt, while CG underwent Standard-Vt. They were assessed weekly throughout the protocol duration. The main finding is represented by no significant differences in weaning duration between groups (IG: 14.5 days, CG: 14 days; $p = 0.7349$). There were no significant differences in FVC values, that improved in both groups ($p = 0.172$). The IG had an increase in mean PIP and an increase in mean Pplat compared with the CG ($p < 0.0001$). The were no significant differences in incidence of adverse pulmonary events (p = NS).
Gutierrez et al. 2010 *J Rehabil Res Dev.*	USA	RCT	$N = 12$	55.00 $\pm$ 17.79	12 M	23.46 $\pm$ 4.69	Cervical C3: 2 C4: 5 C5: 5	AIS A-B A: 4 B: 8	Chronic	Complete: 4 Incomplete: 8	Trendelenburg chest optimization (TCO) 20 mL/kg of IBW session duration: 30 min	Supine chest optimization (SCO) 20 mL/kg of IBW session duration: 30 min	Weaning period	* SBT duration * Pulmonary function	This study reports about 12 SCI patients on MV admitted to ICU (mean age 55.00 $\pm$ 17.79; 100% male; mean BMI: 23.46 $\pm$ 4.69). IG underwent TCO, while CG underwent SCO. The main finding is represented by SBT duration. SBT duration was significantly greater in IG compared to CG (IG: 87.67 $\pm$ 38.42 min vs. CG: 33.50 $\pm$ 30.34 min; $p = 0.001$). There were significant improvements in MValv ($p < 0.003$), VCO_2 ($p < 0.001$), and Cst ($p < 0.002$) in IG following TCO. Moreover, SBT post-TCO was associated with significant improvements in MValv ($p < 0.03$) and RSBI ($p < 0.002$).
Gundogdu et al. 2017 *Disabil Rehabil.*	Turkey	Cohort study	$N = 35$ n-MV: 10 n-TT: 25	MV: 27.1 $\pm$ 16.4 TT: 30.0 $\pm$ 10.3	MV: 9 M/1 F TT: 19 M/6 F	NR	Cervical MV: C1: 3 C2: 1 C3: 1 C4: 2 C5: 2 C6: 1 C7: 0 TT: C1: 0 C2: 0 C3: 2 C4: 7 C5: 9 C6: 4 C7: 3	AIS A-B-C AIS A: 29 AIS B-C: 6	Acute	Complete: 22 Incomplete: 13	*MV group:* Clearance of airway secretions Respiratory muscle training (with threshold IMT device, and was administrated in 10 repetitions, three times a day, five days per week) Swallowing therapy SBT progressively greater in duration and frequency as tolerated TT closure time gradually increased as tolerated	*TT group:* Clearance of airway secretions Ventilator muscle training (with threshold IMT device, and was administrated in 10 repetitions, three times a day, five days per week) Swallowing therapy TT closure time gradually increased as tolerated	Weaning or decannulation period	* Weaning duration * Decannulation time * Pulmonary function	This study reports about 35 SCI patients (mean age: MV: 27.1 $\pm$ 16.4; TT: 30.0 $\pm$ 10.3; MV: 9 male and TT: 19 male), divided into MV group and TT group. The main finding is represented by MV weaning duration, which was 37.0 $\pm$ 11.6 days. The mean duration of decannulation was 31.7 $\pm$ 16.9 days. Seven out of 10 (70%) patients were successfully weaned from MV and 30 out of 35 patients (85.7%) were decannulated. The means of the MIP, MEP and PCF values of MV-dependent patients before/after the weaning protocol significantly improved (MIP: -18.6 ± 11.2 vs. -41.1 ± 18.1, $p = 0.005$; MEP: 19.0 $\pm$ 9.8 vs. 40.0 $\pm$ 13.9, $p = 0.005$; PCF: 46.0 $\pm$ 49.9 vs. 130 $\pm$ 71.3, $p = 0.012$). Pre/post treatment PCF values were also significantly improved in tracheostomized patients ($p < 0.001$).

Table 1, continued

Authors journal year	Nationality	Study design	Participants								Intervention	Comparator	Protocol duration	Outcomes	Main findings
			Sample size	Age (years)	Male/Female	BMI (kg/m2)	Neurological lesion level (Cervical, Thoracic, Lumbar)	AIS	Chronic/ Acute	Complete/ Incomplete					
Hatton et al. 2021 *J Spinal Cord Med.*	USA	Cohort study	$N = 181$ IG: 22 CG: 159	IG: 40 (27–51 IQR) CG: 53 (35–70 IQR)	IG: 17 (77%) M CG: 126 (79%) M	IG: 27 (25–30) CG: 27 (24–31)	Cervical IG: C1: 2 (9%) C2: 3 (14%) C3: 3 (14%) C4: 6 (27%) C5: 5 (23%) C6: 3 (14%) C7: 0 CG: C1: 11 (7%) C2: 26 (16%) C3: 24 (15%) C4: 33 (21%) C5: 42 (26%) C6: 18 (11%) C7: 5 (3%)	NR	Acute	Complete: 77 Incomplete: 104	High-Vt > 10 cc/kg PBW (mean: 10.8 [10.2–11.3 IQR] cc/kg PBW)	Standard-Vt < 10 cc/kg PBW (mean: 7.6 [6.8–8.6 IQR] cc/kg PBW)	NR	* Ventilator dependence at discharge * Safety	This study reports about 181 SCI patients on MV admitted to ICU (mean age IG: 40 [27–51 IQR], CG: 53 [35-70 IQR]; mean BMI: IG: 27 [25–30], CG: 27 [24–31]; IG: 79% male, CG: 77% male). IG underwent to High-Vt, while CG underwent Standard-Vt. The main finding is represented by VAP incidence. In particular, 85 patients (47%) developed VAP (68% of patients in High-Vt group and in 44% of patients in standard tidal volumes group; $p = 0.06$). Ventilator dependence at 30 hospital days or hospital discharge was significantly increased in IG (82% of patients) compared with CG (38% of patients) ($p < 0.001$).
Kim et al. 2007 *Spinal Cord.*	Korea	Cohort study	$N = 62$	47.6 ± 15.8	55 M/7 F	NR	Cervical C-: 1 C1: 3 C2: 9 C3: 23 C4: 20 C5: 2 C6: 2 C7: 0 C8: 2	AIS A-B A: 49 B: 13	Acute	Complete: 49 Incomplete: 13	* Tracheal suctioning (MAC and manually assisted cough by abdominal thrust) whenever necessary or at least every 2 h	/	Weaning period	* Weaning success rate * Duration from tracheostomy to decannulation	This study reports about 62 SCI patients on MV (mean age: 47.6 ± 15.8; 55 male). IG underwent continuous MV, MAC, and tracheal suctioning. The main finding is represented by ventilator weaning successfully after extubation/decannulation. All patients succeeded in decannulation/extubation after the rehabilitation program. Fifteen patients totally weaned off from ventilators after NIV. Mean time from tracheostomy to decannulation was 7.0 ± 14.5 months.
Korupolu et al. 2021 *Spinal Cord.*	USA	Cohort study	$N = 84$ IG: 34 CG: 50	IG: 43 (26–59 IQR) CG: 33 (21–56 IQR)	IG: 24 (71 %) M CG: 41 (82%) M	NR	Cervical and thoracic IG: C1-C3: 11 (32%) C4-C6: 22 (65%) CG: C1-C3: 22 (44%) C4-C6: 25 (50%) T2-T4: 2 (4%) Unknown: 1 (2%)	AIS A-B-C-D IG: A: 19 (56%) B: 7 (20.5%) C: 7 (20.5%) D: 0 Unknown: 1 (3%) CG: A: 30 (60%) B: 9 (18%) C: 7 (14%) D: 2 (4%) Unknown: 2 (4%)	Acute	Complete: 49 Incomplete: 35	High-Vt 15–20 ml/kg PBW	Standard-Vt 8.4–14.9 ml/kg PBW	Weaning period	* Weaning duration * MV duration * Weaning success rate * Length of stay * Safety	This study reports about 84 SCI patients on MV (mean age: IG: 43 [26–59 IQR], CG: 33 [21–56 IQR]; IG: 71 % male, CG: 82% male). IG underwent to High-Vt, while CG underwent Standard-Vt. The main finding is represented by the incidence of pneumonia. The risk of pneumonia in IG was 4.3 times higher compared to CG (95%; CI: 1.5–12). Odds of pulmonary adverse events in IG were 5.4 times higher (CI: 1.8–17) compared to CG. There were no significant improvements in weaning duration (IG: 19 [18, 22 IQR]; CG: 19 [18, 21 IQR]; $p = 0.9$), weaning success (IG: 28 (82%); 45 (90%); $p = 0.31$) preweaning days (IG: 13 [9–19 IQR]; CG: 9 [6–17 IQR]; $p = 0.15$), or length of stay (IG: 49 [38–65 IQR]; CG: 45 [39–68 IQR]; $P = 0.7$) between the two groups.
McCaughey et al. 2015 *PLoS One.*	UK	Cohort study	$N = 19$ IG: 10 CG: 9	IG: 48.2 ± 18.0 CG: 47.8 ± 20.2	IG: 8 M/2 F CG: 8 M/1 F	NR	Cervical IG: C0/5: 1 C3/4: 2 C4: 3 C5: 1 C5/6: 1 C6/7: 1 C7: 1 CG: C3: 1 C4: 2 C5: 5 C6: 1	AIS A-B-C IG: A: 5 B: 2 C: 3 CG: A: 7 B: 1 C: 1	Acute	Complete: 12 Incomplete: 7	Abdominal Functional Electrical Stimulation *Frequency:* 5 sessions /week on 4 alternate weeks *Volume:* 20–40 minutes/session	Usual care	8 weeks	* Weaning duration * Pulmonary function	This study reports about 19 SCI patients on MV (mean age: IG: 48.2 ± 18.0, CG: 47.8 ± 20.2; IG: 8 male, CG: 8 male). IG underwent abdominal functional electrical stimulation compared to usual care. The main finding is that weaning duration of IG was 33 ± 14 days, while the weaning duration in CG was 44 ± 24 days, without differences between groups ($p = 0.41$). Significant differences were reported in terms of VT ($p <$ 0.00). VC increased significantly in IG (12.6 mL/kg to 18.7 mL/kg; $p < 0.005$).

Table 1, continued

Authors journal year	Nationality	Study design	Participants: Sample size	Age (years)	Male/Female	BMI (kg/m2)	Neurological lesion level (Cervical, Thoracic, Lumbar)	AIS	Chronic/ Acute	Complete/ Incomplete	Intervention	Comparator	Protocol duration	Outcomes	Main findings
Peterson et al. 1999 *Spinal Cord.*	USA	Cohort study	$N = 42$ IG: 19 CG: 23	IG: 31 ± 13.85 CG: 29 ± 11.86	37 M/5 F	NR	Cervical C3-C4	NR	Acute	Complete	High-Vt Mean 25.3 ml/kg (range 20.3–32.2 ml/kg)	Low-Vt Mean 15.5 ml/kg (range 11.6–19.4 ml/kg)	Weaning period	* Weaning duration * Safety	This study reports about 42 SCI patients on MV (mean age: IG: 31 ± 13.85, CG: 29 ± 11.86; 37 male). IG underwent to High-Vt, while CG underwent Low-Vt. The main finding is represented by weaning duration. The IG had a significant improvement in weaning time compared to CG (37.6 days vs 58.7 days; $p = 0.02$). There were significant differences between groups in pulmonary complications outcomes. The IG had significantly less atelectasis ($P = 0.01$) compared to CG.
Wong et al. 2012 *Top Spinal Cord Inj Rehabil.*	USA	Cohort study	$N = 24$	33.4 ± 16.6	22 M/2 F	25.82 ± 16.6	Cervical C1: 7 C2: 1 C3: 4 C4: 12	AIS A-B-C-D A: 19 B: 3 C: 1 D: 1	Acute	Complete: 19 Incomplete: 5	* High-Vt 12–15 ml/kg IBW * Secretion management (HFPV and MIE) every 2 to 4 hours, for 30 to 45 minutes.	/	Weaning period	* Weaning duration	This study reports about 24 SCI patients on MV (mean age: 33.4 ± 16.6; mean BMI: 25.82 ± 16.6; 22 male). IG underwent to High-Vt. The main finding is represented by weaning duration. Fourteen patients were weaned off the ventilator, the average day to be weaned from the time of admission was 27.6 ± 12.9 days. For a majority of these patients, respiratory improvements were noted within 1 week of admission to our SCI unit.
Atito-Nahr et al. 2008 *British Journal of Intensive Care*	UK	Case series	$N = 13$	43.8 ± 18	10 M/3 F	NR	Cervical and Thoracic C2: 2 C3: 4 C4: 5 C5: 1 C6: 1 T4: 1	AIS A-B-C A: 9 B: 1 C: 3	Acute	Complete: 9 Incomplete: 4	* Ventilatory support (night: CMV 10–15 ml/kg; day: PC SIMV ± PS ∼ 25 cmH20) * Tracheal cuff deflation * Mobilisation of secretions with pressure monitored hyperinflation * Routine bagging * Positioning (physical turns from side to side and back 3–4 hourly and mobilise in wheelchair) * Swallowing and speech therapy * Progressive SBT * Speaking valve and deflate cuff if present, * Monitor vital capacity, combined with incentive spirometry, supine position initially)	/	Weaning period	* Weaning duration * Pulmonary function	This study reports about 13 SCI patients on MV (mean age: 43.8 ± 18; 10 male). IG underwent ventilatory support, tracheal cuff deflation, chest physiotherapy, routine bagging, positioning, swallowing and speech therapy, and weaning protocol. The main finding is represented by weaning duration. The mean weaning duration was 56.1 ± 65.9 days (39.5 ± 28.9 days excluding patients with higher lesion or phrenic nerve paresis). Average value of VC on admission was 501.4 ml, final average was 1,415.4 ml.
Duarte et al. 2021 *Spinal Cord Ser Cases.*	Brazil	Case series	$N = 10$ IG: 4 CG: 6	IG: 28 ± 14 CG: 29 ± 5	IG: 75% M/25% F CG: 83% M/16% F	NR	Cervical C3: 1 C2/4: 1 C4/5: 3 C4/6: 1 C5/6: 3 C6/7: 1	AIS A	Acute	Complete	Transcutaneous electric diaphragmatic stimulation *Setting*: frequency of 30 hertz, pulse width of 1 ms, rise time of 0.7 ms, and current intensity of 60 milliamps *Frequency*: 2 sessions/ day for 7 days a week *Duration (session)*: 20 min	Standard weaning protocol	Weaning period	* Weaning duration * MV duration * Length of stay	This study reports about 10 SCI patients on MV admitted to ICU (mean age IG: 28 ± 14 CG: 29 ± 5; IG: 75% male, CG: 83% male). IG underwent transcutaneous electric diaphragmatic stimulation, while CG underwent standard weaning program. The main finding is represented by the weaning duration (IG: 28 ± 15 days; CG: 50 ± 19 days). Moreover, there were differences in total MV duration (IG: 33 ± 15 days; CG: 60 ± 22 days) and length of stay in ICU (IG: 31 ± 18 days; CG: 63 ± 45 days).

Table 1, continued

Authors journal year	Nationality	Study design	Participants: Sample size	Participants: Age (years)	Participants: Male/Female	Participants: BMI (kg/m2)	Participants: Neurological lesion level (Cervical, Thoracic, Lumbar)	Participants: AIS	Participants: Chronic/ Acute	Participants: Complete/ Incomplete	Intervention	Comparator	Protocol duration	Outcomes	Main findings
Gutierrez et al. 2003 *J Rehabil Res Dev.*	USA	Case series	$N = 7$	Range: 44–68	7 M	NR	Cervical C2: 2 C4: 1 C5: 2 C5-7: 1 C7: 1	NR	Chronic	Incomplete	Resistance and endurance protocol: ∗ *Pretraining Optimization* (Position, Suction, Aerosolize, Hyperinflate) ∗ *Inspiratory/Expiratory Resistance Training* (Inspiratory/expiratory trainer, Cuff deflated and red cap on trach tube) ∗ *On-Vent Endurance Training* (SIMV rate of 1–2, PS to maintain ∼400 cc, Progress to off-vent training when patient maintains a tidal volume = 400 ml on CPAP 5 PS 5 for 2 continuous hours per day for 1 week) ∗ *Off-Vent Endurance Training* (Gas injection nebulizer wye-piece as tolerated, Tracheal gas insufflation device as tolerated, Red cap to trach tube as tolerated, Tracheal decannulation unless contraindicated)	/	Weaning period	∗ Weaning success rate ∗ Pulmonary function	This study reports about 7 SCI patients on MV (age range: 44–68; 100% male) undergoing resistance and endurance protocol. The main findings are represented by weaning success rate. Low tetraplegic patients completed their prescribed training. Of these, 4/4 (100%) were weaned from mechanical ventilation. Significant changes were reported in terms of MIP ($p = 0.001$), PEmax ($p = 0.002$), and VC ($p = 0.001$). Moreover, significant improvements were reported in terms of on-vent endurance ($p = 0.001$) and off-vent breathing ($p = 0.013$).
Toki et al. 2008 *Arch Phys Med Rehabil.*	Japan	Case series	$N = 2$	Case 1: 34 Case 2: 29	Case 1: M Case 2: M	NR	Cervical Case 1: C1 Case 2: C1	Case 1: A Case 2: A	Acute	Complete	NPPV Noninvasive Positive-Pressure Ventilation Case 1: starting from Vt IBW of 9.5 mL/kg Case 2: starting from Vt IBW of 7.8 mL/kg	/	Hospitalization time	∗ Pulmonary function ∗ Length of stay	This study reports about 2 SCI patients on MV undergoing NPPV. Both patients were discharged home successfully. At first, they were ventilated through tracheostomy tube, and then were decannulated to NPPV. Improvements were reported in terms of: Vc (Case 1 = pre: 50 mL vs. post: 500 mL; Case 2 = pre: NS vs. post: 670 mL); Vt (Case 1 = pre: 670 mL vs. post: 1400 mL; Case 2 = pre: 550 vs. post: 1500 mL); Respiratory rate (Case 1 = pre: 14/min vs. post: 12/min; Case 2 = pre: 6/min vs. post: 12/min); Maximum insufflation capacity (final = Case 1:2600 mL; Case 2: 2150 mL).

Table 1, continued

Authors journal year	Nationality	Study design	Participants								Intervention	Comparator	Protocol duration	Outcomes	Main findings
			Sample size	Age (years)	Male/Female	BMI (kg/m2)	Neurological lesion level (Cervical, Thoracic, Lumbar)	AIS	Chronic/ Acute	Complete/ Incomplete					
Zhang et al. 2020 *Signa Vitae*	China	Case report	$N = 1$	48	M	NR	Cervical C4	A	Acute	Complete	* IMT * passive training (stretching of the intercostal muscles, bed tilting, passive movement of the scapula and the proximal end of the upper limbs) * active training (various diaphragmatic facilitation techniques)	/	Weaning period	* Weaning success rate * SBT duration * Pulmonary function	This study reports about a male SCI patient on MV (age: 48), with complete cervical spinal cord injury (level C4). The patient underwent IMT. The patient was successfully weaned from mechanical ventilation and discharged from the hospital. The MIP increased to 31.05 cmH2O (vs. 13.88 cmH2O pre-intervention. The diaphragmatic muscle showed a thickness of 0.22 cm (at the admission was 0.17 cm) and a diaphragmatic activity of 2.22 cm (at the admission was 4 cm).

Abbreviations: AIS = Asia Impairment Scale; BMI = body mass index; CG = Control group; CI = confidence interval; CMV = Continuous mandatory ventilation; Cst = static chest compliance; FVC = forced vital capacity; HFPV = High frequency percussive ventilation; High-Vt = High Tidal Volume; IBW = ideal body weight; IG = Intervention group; IQR = interquartile range; MAC = mechanically assisted coughing; MIE = mechanical insufflation-exsufflation; MIP = maximal inspiratory pressure; MV = mechanical ventilation; MValv = alveolar minute volume; NIV = non-invasive mechanical ventilation; NPPV = Noninvasive Positive-Pressure Ventilation; NR = not reported; NS = not significant; PBW = predicted body weight; PEmax = maximal expiratory pressure; PC = pressure controlled; PIP = Peak inspiratory pressure; Pplat = Plateau pressure; PS = pressure support; RSBI = rapid shallow breathing index; SBT = Spontaneous Breathing Trial; SCI = Spinal cord injury; SIMV = Synchronized Intermittent Mandatory Ventilation; Standard-Vt = Standard Tidal Volume; TT = tracheostomy tube; VAP = ventilator-associated pneumonia; VC = vital capacity; VCO_2 = CO2 Elimination.

included physical turns from side to side and back 3–4 hourly and mobilise in wheelchair.

- *Respiratory muscles training*: Three [40,41,53] studies assessed respiratory muscle training proposing different therapeutic strategies. In particular, the case series of Gutierrez et al. [41] assessed the effect of a resistance and endurance training protocol including 4 phases (pretraining optimization, inspiratory/expiratory resistance training, on-vent endurance training, and off-vent endurance training). On the other hand, Zhang et al. [53] assessed the effect of an inspiratory muscle training protocol. In particular, it was composed of passive activities (stretching of the intercostal muscles, bed tilting, passive movement of the scapula and the proximal end of the upper limbs), and strength and endurance training on the diaphragm. Lastly, Gundogdu et al. [40], assessed the effect of an inspiratory muscle training protocol with a threshold IMT device, administered in 10 repetitions, three times a day, five days per week until decannulation.
- *Abdominal or diaphragmatic electrical stimulation*: Electrical stimulation was assessed in two studies [38,46]. Duarte et al. [38] assessed the effects of transcutaneous electric diaphragmatic stimulation (TEDS) administrated for 20 minutes per session, twice a day, for 7 days a week. TEDS was administrated with a frequency of 30 hertz, pulse width of 1 ms, rise time of 0.7 ms, and current intensity of 60 milliamps. McCaughey et al. [46] assessed the effects of Abdominal Functional Electrical Stimulation (AFES), 20–40 minutes per session, five sessions per week on 4 alternate weeks, for 8 weeks.
- *Lung hyperinflation/recruitment maneuvers*: Gutierrez et al. [41,42] and Atito-Narh et al. [37] assessed lung hyperinflation maneuvers with ventilators or manual resuscitation bag.
- *Secretion management (including tracheal suctioning and swallowing rehabilitation)*: Four studies [37,40,44,52] assessed the effects of secretion management, clearance of airway, swallowing therapy, or tracheal suctioning. In particular, Kim et al. [44] assessed the effects of mechanical insufflation-exsufflation (MI-E) or manually assisted cough (MAC) by abdominal thrust followed by suctioning or self-oral expectoration. Similarly, Wong et al. [52] assessed the effects of high-frequency percussive ventilation (HFPV) and mechanical insufflation-exsufflation (MI-E) for managing secretion, every 2–4 hours, for 30 to 45 minutes.

Interestingly, Atito-Narh et al. [37] included swallowing rehabilitation in their protocol, consisting of bedside assessment of swallow performance with deflated cuff before administering oral intake. Moreover, in the study by Gundogdu et al. [40] patients received daily care for oral hygiene, thermal (cold) and tactile stimulation, head and trunk positioning, dietary modification, swallowing maneuvers and oral motor exercises, including the lip, tongue and jaw movements according to the different patient characteristics for 60 min a day, 5 days a week for 3 to 6 weeks.

All rehabilitation programs assessed in the present systematic review have been summarized in detail in Table 1.

3.3. *Control characteristics*

The intervention groups were compared with standard/low volume mechanical ventilation [39,43,45,47], usual care/standard weaning protocol [38,46], or positioning [42]. In particular, in the RCT performed by Gutierrez et al. [42], the intervention group, which performed Trendelenburg chest optimization (TCO), was compared with Supine Chest Optimization (SCO), setting the Vt on 20 mL/kg of ideal body weight for 30 min per session. All control protocols assessed in the present systematic review have been summarized in Table 1.

3.4. *Primary Outcomes – Weaning duration, MV duration, and weaning success rate*

Weaning duration has been assessed in eight trials [37–40,45–47,52], two studies [38,45] assessed MV duration, and four studies [41,44,45,53] assessed weaning success rate. More in detail, the RCT performed by Fenton et al. [39] showed no significant differences in mean days to wean between high-Vt group and standard-Vt group (IG: 14.5 days, CG: 14 days; $p = 0.7349$). In contrast, Peterson et al. [47] showed that the high-Vt group had a significant improvement in weaning time compared to low-Vt group (IG: 37.6 days; CG: 58.7 days; $p = 0.02$). In the cohort study by Gundogdu et al. [40], mean weaning duration was 37.0 ± 11.6 days, and seven out of 10 (70%) patients were successfully weaned from MV. Moreover, in the cohort study by Korupolu et al. [45], there were no significant differences in weaning duration (IG: 19 [18, 22 IQR]; CG: 19 [18, 21 IQR]; $p = 0.9$), weaning success rate (IG: 28 (82%); 45 (90%); $p = 0.31$), and total MV days

(IG: 35 [26–47 IQR]; CG: 32 [26–39 IQR]; $p = 0.18$) between high-Vt group (IG) and standard-Vt group (CG). On the other hand, they underlined increased risk of pneumonia and higher odds of pulmonary adverse events. Similarly, Hatton et al. [43] showed a tendency to an association between high Vt MV and increased ventilators associated pneumonia ($p = 0.06$) and a longer ventilator dependence ($p < 0.001$). In their cohort study, McCaughey et al. [46] showed no significant differences in weaning duration between AFES group and usual care group (IG: 33 $\pm$ 14 days; CG: 44 $\pm$ 24 days; $p = 0.41$). Interestingly, Duarte et al. [38] underlined weaning duration was lower in patients undergoing TEDS compared to standard weaning protocol (28 $\pm$ 15 days vs 50 $\pm$ 19 days). In addition, there were differences in total MV duration (IG: 33 $\pm$ 15 days; CG: 60 $\pm$ 22 days). Unfortunately, p-values were not reported for statistical comparison.

In the case series by Atito-Narh et al. [37] assessing the effects of a comprehensive rehabilitation approach (ventilatory support, tracheal cuff deflation, mobilization of secretions with pressure monitored hyperinflation, routine bagging, positioning, swallowing and speech), the mean weaning duration was 56.1 $\pm$ 65.9 days.

Wong et al. [52] assessed the effects of high-Vt, MIE and HFPV, 13 (neurological levels C3-C4) were successfully weaned from MV, nine with level of injury at C1, C2, and C3 were not weaned, one patient with C4 AIS B needed night-time ventilation. Gutierrez et al. [41] reported that all tetraplegic patients with low neurological levels and completing the prescribed training underwent successful weaning from MV. Kim et al. [44] showed a weaning success rate of 24.2% in patients with cervical spinal cord injury. Lastly, Zhang et al. [53] reported successful weaning from MV in the patient that underwent to IMT program.

3.5. Secondary outcomes – pulmonary function

Pulmonary function was assessed in eight studies [37, 39–42,46,50,53]. In particular, in the RCT by Fenton et al. [39], no significant differences between groups were reported in terms of FVC values. However, significant within-group differences were reported in both groups ($p = 0.172$). On the other hand, the high-Vt group had a significant increase in mean PIP and mean Pplat compared with the standard-Vt group ($p < 0.0001$).

Concurrently, the RCT by Gutierrez et al. [42] underlined that Spontaneous Breathing Trial (SBT) duration was significantly longer in TCO group compared to SCO group (IG: 87.67 $\pm$ 38.42 min vs. CG: 33.50 $\pm$ 30.34 min; $p = 0.001$). Moreover, there were significant improvements in alveolar minute volume ($p < 0.003$), CO_2 elimination ($p < 0.001$), and chest static compliance ($p < 0.002$) in TCO group.

In the cohort study by Gundogdu et al. [40], the means of the maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP) and peak cough flow (PCF) values of MV-dependent patients after the weaning protocol significantly improved (MIP: -18.6 ± 11.2 vs. -41.1 ± 18.1, $p = 0.005$; MEP: 19.0 $\pm$ 9.8 vs. 40.0 $\pm$ 13.9, $p = 0.005$; PCF: 46.0 $\pm$ 49.9 vs. 130 $\pm$ 71.3, $p = 0.012$). Post treatment PCF values were also significantly improved in tracheostomized patients ($p < 0.001$). McCaughey et al. [46] reported significant differences in terms of Vt ($p < 0.001$), vital capacity (VC) (12.6 mL/kg to 18.7 mL/kg; $p < 0.005$) in AFES group. Concurrently, Atito-Narh et al. [37] showed that the mean value of VC on admission was 501.4 ml compared to 1,415.4 ml after the treatment. In the case series of Gutierrez et al. [41] all patients significantly improved in terms of MIP ($p = 0.001$), maximal expiratory pressure (PEmax) ($p = 0.002$), VC ($p = 0.001$), on-vent endurance ($p = 0.001$), and off-vent breathing ($p = 0.013$). In accordance, Toki et al. [50] reported improvements in VC, Vt, respiratory rate, maximum insufflation capacity after the rehabilitation protocol. The case report of Zhang et al. [53] reported a consistent increase in MIP (13.88 cmH_2O vs 31.05 cmH_2O). The diaphragmatic muscle showed a thickness of 0.22 cm (at the admission was 0.17 cm) and a diaphragmatic activity of 2.22 cm (at the admission was 4 cm).

3.6. Secondary outcomes – extubation or decannulation

In the cohort study by Gundogdu et al. [40], the mean duration of decannulation was 31.7 $\pm$ 16.9 days, and 30 of 35 (85.7%) patients were decannulated. Kim et al. [44] showed that all patients succeeded in decannulation/extubation after employing mechanically assisted coughing and NIV. Mean time from tracheostomy to decannulation was 7.0 $\pm$ 14.5 months.

3.7. Secondary outcomes – length of stay

The study by Duarte et al. [38] reported differences in length of stay in ICU between TEDS group and standard weaning protocol group (IG: 31 $\pm$ 18 days; CG: 63 $\pm$ 45 days).

Table 2
Joanna Briggs Institute Critical Appraisal Checklist for the studies included

Joanna Briggs Institute Critical Appraisal Checklist for RCTs

Authors and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total score
Fenton et al. 2016	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	11
Gutierrez et al. 2010	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	12

Joanna Briggs Institute Critical Appraisal Checklist for RCTs: Q1 = Was true randomization used for assignment of participants to treatment groups?; Q2 = Was allocation to treatment groups concealed?; Q3 = Were treatment groups similar at the baseline?; Q4 = Were participants blind to treatment assignment?; Q5 = Were those delivering treatment blind to treatment assignment?; Q6 = Were outcomes assessors blind to treatment assignment?; Q7 = Were treatment groups treated identically other than the intervention of interest?; Q8 = Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?; Q9 = Were participants analyzed in the groups to which they were randomized?; Q10 = Were outcomes measured in the same way for treatment groups?; Q11 = Were outcomes measured in a reliable way?; Q12 = Was appropriate statistical analysis used?; Q13 = Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?; N = no, Y = yes; N/A = not applicable.

Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies

Authors and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total score
Gundogdu et al. 2016	Y	N/A	Y	N	N	Y	Y	Y	Y	N	Y	7
Hatton et al. 2021	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	N	Y	8
Kim et al. 2007	Y	N/A	Y	Y	N	Y	Y	Y	Y	N	Y	8
Korupolu et al. 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
McCaughey et al. 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Peterson et al. 1999	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Wong et al. 2012	Y	N/A	Y	Y	N	Y	Y	Y	Y	N	Y	8

Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies: Q1 = Were the two groups similar and recruited from the same population?; Q2 = Were the exposures measured similarly to assign people to both exposed and unexposed groups?; Q3 = Was the exposure measured in a valid and reliable way?; Q4 = Were confounding factors identified?; Q5 = Were strategies to deal with confounding factors stated?; Q6 = Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?; Q7 = Were the outcomes measured in a valid and reliable way?; Q8 = Was the follow up time reported and sufficient to be long enough for outcomes to occur?; Q9 = Was follow up complete, and if not, were the reasons to loss to follow up described and explored?; Q10 = Were strategies to address incomplete follow up utilized?; Q11 = Was appropriate statistical analysis used?; N = no, Y = yes; N/A = not applicable.

Joanna Briggs Institute Critical Appraisal Checklist for Case Series

Authors and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total score
Atito-Nahr et al. 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Duarte et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Gutierrez et al. 2003	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	9
Toki et al. 2008	Y	Y	Y	N	Y	Y	Y	Y	N	Y	8

Joanna Briggs Institute Critical Appraisal Checklist for Case Series: Q1 = Were there clear criteria for inclusion in the case series?; Q2 = Was the condition measured in a standard, reliable way for all participants included in the case series?; Q3 = Were valid methods used for identification of the condition for all participants included in the case series?; Q4 = Did the case series have consecutive inclusion of participants?; Q5 = Did the case series have complete inclusion of participants?; Q6 = Was there clear reporting of the demographics of the participants in the study?; Q7 = Was there clear reporting of clinical information of the participants?; Q8 = Were the outcomes or follow up results of cases clearly reported?; Q9 = Was there clear reporting of the presenting site(s)/clinic(s) demographic information?; Q10 = Was statistical analysis appropriate?; N = no, Y = yes; N/A = not applicable.

Joanna Briggs Institute Critical Appraisal Checklist for Case Reports

Authors and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total score
Zhang et al. 2020	N	N	Y	Y	Y	Y	Y	Y	6

Joanna Briggs Institute Critical Appraisal Checklist for Case Reports: Q1 = Were patient's demographic characteristics clearly described?; Q2 = Was the patient's history clearly described and presented as a timeline?; Q3 = Was the current clinical condition of the patient on presentation clearly described?; Q4 = Were diagnostic tests or assessment methods and the results clearly described?; Q5 = Was the intervention(s) or treatment procedure(s) clearly described?; Q6 = Was the post-intervention clinical condition clearly described?; Q7 = Were adverse events (harms) or unanticipated events identified and described?; Q8 = Does the case report provide takeaway lessons?; N = no, Y = yes; N/A = not applicable.

3.8. *Secondary outcomes – ventilator dependence at discharge*

Hatton et al. [43] showed that ventilator dependence at 30 hospital days or hospital discharge was significantly increased in high-Vt group (82% of patients) compared with standard-Vt group (38% of patients) ($p < 0.001$).

3.9. *Secondary outcomes – safety*

The RCT by Fenton et al. [39] reported no significant differences in incidence of adverse pulmonary events (p =NS). Hatton et al. [43] showed that, in total, 85 patients (47%) developed VAP. In particular, VAP developed in 68% of patients ($n = 15$) receiving high-Vt and in 44% ($n = 70$) receiving standard-Vt ($p = 0.06$). The cohort study by Korupolu et al. [45] underlined significant differences in risk of pneumonia between high-Vt group and standard-Vt group. The risk of pneumonia in IG was 4.3 times higher compared to CG (95%; CI: 1.5–12). Odds of pulmonary adverse events in IG were 5.4 times higher (CI: 1.8–17) compared to CG. In contrast, Peterson et al. [47] reported significant differences between high-Vt group and standard-Vt group in pulmonary complications outcomes. The high-Vt group had significantly less atelectasis ($P = 0.01$) compared to standard-Vt group.

3.10. *Quality assessment*

The quality assessment was performed following the Joanna Briggs Institute Critical Appraisal Checklist for Randomized Controlled Trials, JBI Critical Appraisal Checklist for Cohort Studies, JBI Critical Appraisal Checklist for Case Series, or JBI Critical Appraisal Checklist for Case Reports basing on the study design [36]. The studies included [39,40,42–47,52,53] presented at least one serious risk of bias, which translated into an overall serious risk of bias for that study. The main quality concerns included the lack of data on baseline characteristics of study participants, non-random sampling approaches (convenience samples), missing data, and lack of a reliable tool to estimate and report outcomes. Further details about the quality assessment of each study included in this review are shown in Table 2.

4. Discussion

To date, rehabilitation could be considered as a milestone in the complex management of SCI patients [54–56], with several studies proposing different approaches to enhance the weaning process in mechanically ventilated SCI patients [37–53]. However, the optimal rehabilitation approach is still a challenge for physicians and researchers, considering that no clear indications are currently available for mechanically ventilated SCI patients.

Therefore, by this systematic review we aimed at providing a broad overview about the current rehabilitation strategies aiming at optimizing the weaning process of these patients, characterizing the specific rehabilitation approaches in order to reduce the weaning duration, improve functional outcomes and minimize MV related complications.

Interestingly, six main rehabilitative strategies have been identified in the scientific literature: i) high-Vt ventilation, ii) positioning, iii) mechanical lung recruitment maneuvers, iv) secretion management strategies, v) respiratory muscle training, and vi) electrical stimulation.

To date, high-VT ventilation in patients with SCI is commonly used in the clinical practice [57] and supported by specific guidelines [58]. In this context, SCI patients were frequently not affected by chronic pulmonary conditions, and “healthy lungs” should not be damaged by relatively high-volume ventilation. Moreover, a tidal volume of up to 1000 ml may represent approximately 30% of the normal inspiratory capacity of a healthy adult [29]. In addition, higher VTs stretch the airways smooth muscles, and promote the production of pulmonary surfactant, the alveolar surface tension with positive implications in the prevention of peripheral collapse of small airways [52]. Our results identified five studies [39,43,45,47,52] assessing the role of high-Vt compared to low-Vt, highlighting conflicting results. More in detail, two retrospective analyses [47,52] supported higher VTs (more than 20 ml/kg IBW), suggesting positive implications for weaning process duration and complications rate. In addition, Wong et al. [52] suggested that higher VTs might optimize the respiratory status, vocalization, and participation in rehabilitation programs of patients with SCI, reducing MV duration. On the other hand, it should be noted that all patients underwent a comprehensive pulmonary rehabilitation program including HFPV, MIE and high-VT ventilation. Therefore, it is impossible to draw conclusions about each single rehabilitation intervention. On the contrary, the RCT by Fenton et al. [39] confirmed the safety of high-Vt ventilation (20 ml/kg vs 10 ml/kg IBW), without reporting difference in the weaning duration. Lastly, the more recent studies by Hatton et al. [43] and Korupolu et al. [45] raised doubt about the safety of this rehabilitation approach, since no advantages in weaning duration were found and a higher incidence of pneumonia and pulmonary adverse events were reported. Surprisingly, both studies did not report any interventions for the management of mucus encumbrance or other interventions aimed to prevent secretion stagnation and atelectasis [43,45].

Altogether, these results underlined some concerns about the effectiveness of high-Vt ventilation. Despite these considerations, high-Vt ventilation should not be proposed alone, but included in a comprehensive rehabilitation intervention targeting the multilevel pulmonary impairment of patients with SCI.

In contrast, secretion management strategies were described in four studies [37,40,44,52] reporting promising results in terms of weaning duration [37,40,52] or weaning success rate [44]. Despite the positive data, no study assessed the role of secretion management strategies without other interventions.

Although positioning techniques play a key role in the management of patients with SCI due to their widely documented role in secondary complications prevention [59], only two studies [37,42] assessed mobilization/positioning as a potential treatment for improving weaning of SCI patients. Intriguingly, the RCT by Gutierrez et al. [42] reported significant differences in patients undergoing Trendelenburg positioning compared to supine chest optimization in terms of SBT duration. However, no significant results were reported in terms of weaning duration and weaning success rate, probably due to the small sample size. On the other hand, the case series from Atito-Nahr et al. [37] reported positive results of a specific positioning protocol included in a comprehensive rehabilitation approach. Further studies might clarify the role of different positioning in the complex rehabilitation program also improving pressure ulcer risk, joint contractures, swallowing optimization and several other disabling conditions that might benefit from positioning or repositioning techniques [60–64].

Interestingly, respiratory muscle training has been assessed by three studies [40,41,53]. In this scenario, a growing interest is rising in the current literature about the role of IMT in prolonged MV. In particular, the recent systematic review and meta-analysis by Vorona et al. [65] highlighted that IMT might be considered a key component of a comprehensive rehabilitation intervention aiming at optimizing weaning duration in difficult-to-wean patients [65]. However, neurological impairment characterizing SCI patients might drastically affect respiratory muscle recruitment and respiratory mechanics [28,29,66], with detrimental consequences on respiratory muscle's response to training. Our results underlined that respiratory muscle training might improve weaning duration [40] or weaning success rate [41,53]. Despite these considerations, a precise patient's stratification is mandatory in a specific IMT that should be tailored to SCI level and SCI completeness, along with a precise inspiratory muscle weakness assessment.

To overcome the neurological deficit affecting respiratory muscle recruitment, two studies [38,46] assessed the effects of electrical stimulations on the diaphragmatic muscle and abdominal muscles. On the other hand, it should be noted that several concerns are still open in the current literature about electrical stimulation in pulmonary rehabilitation and no strong evidence currently support this technique [31,67]. However, electrical stimulations might be considered a suitable rehabilitation strategy in patients with low compliance levels or with high grade of neurological impairment to prevent muscle atrophy.

Taken together, our findings underlined that most of the studies included in the present review assessed different combinations of pulmonary rehabilitation strategies, integrated in a comprehensive rehabilitation intervention. In this scenario, it has been proposed that a multitarget approach might have a role in implementing the synergisms between different therapeutic interventions, with positive effects on functional outcomes of patients with a pulmonary function impairment [27,68].

On the other hand, recent research is now focusing on a precise stratification based on patients' characteristics. In particular, the review by Schreiber et al. [30] recently assessed the factors potentially related to successful weaning and weaning duration in patients with SCI. Interestingly, the authors underlined that It might be partly related to specific consequences on muscle recruitment and ventilation mechanics, which might be significantly influenced by patient's SCI level and SCI completeness [30]. Moreover, presence of multiple spinal cord lesions and pulmonary comorbidities might be crucial factors that might affect weaning process [30]. In this scenario, a patient-tailored approach should consider these issues in order to better personalize the rehabilitative intervention of patients with SCI. Thus, we deeply characterized the participants of this study to provide a qualitative synthesis about the effectiveness of a precise intervention specific to the patient's characteristics. To the best of our knowledge, this is the first systematic review that assessed the effects of a pulmonary rehabilitation approach in weaning from MV of patients with SCI, focusing on specific rehabilitation strategies to promote pulmonary function recovery and minimize complications.

Besides these considerations, we are aware that this review is not free from limitations. Firstly, the low number of the study included, and the heterogeneous study design did not allow to draw strong conclusions. However, it should be noted that these results reflect the currently available literature. More in detail, our findings underlined a large gap of knowledge in this field with current evidence still based on low-quality studies with controversial results. In addition, several questions are still open about the optimal rehabilitation approach since most of the rehabilitation strategies have been studied in a comprehensive approach. Moreover, the type of SCI lesion might severely influence the rehabilitation response and functional outcomes. On the other hand, the studies identified by the present review underlined a large heterogeneity of the study participants in terms of AIS classification which might severely limits the implications of the study's results. In this context, a deeper patient stratification should be considered to address the needing for rehabilitative interventions tailored to patients' characteristics.

5. Conclusions

Rehabilitation strategies with specific indications for patients with SCI are mandatory to prevent severe complications but also to enhance functional recovery and reduce assistance costs in patients with SCI. The results of the present systematic review supported the effects of a comprehensive rehabilitation approach that might include high-Vt ventilation, positioning, mechanical lung recruitment maneuvers, secretion management, respiratory muscle training and electrical stimulation. Despite the promising results, good-quality studies are mandatory to better characterize the effects of specific rehabilitation interventions reducing MV duration. Moreover, a better patients' stratification is needed to optimize the weaning process and better address the clinical need for an evidence-based patient-tailored rehabilitation plan for these subjects.

Ethical approval

Not applicable.

Funding

The authors report no funding.

Informed Consent

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

The authors want to thank Enrico Cavallo for his support to this work.

Author Contributions

Conceptualization, L.L., A.d.S., and M.I.; methodology, L.L., A.d.S., and M.I.; investigation, L.L., F.D.A., A.F., and A.T.; writing – original draft preparation, L.L. and F.D.A.; writing – review and editing, A.d.S and M.I.; visualization, A.F., A.T., C.C., and A.A.; supervision, A.d.S. and M.I. All authors have read and agreed to the published version of the manuscript.

Supplementary data

The supplementary files are available to download from http://dx.doi.org/10.3233/BMR-220201.

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