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Pulmonary rehabilitation in high cervical spinal cord injury: a series of 133 consecutive cases

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STUDY DESIGN: This is a retrospective study.
OBJECTIVES: To detail respiratory management after a high cervical spinal cord injury (HCSCI).
SETTING: A tertiary university hospital's pulmonary rehabilitation center to which most individuals with HCSCI and ventilatory insufficiency throughout Korea are referred.
METHODS: The medical records of individuals with complete or sensory incomplete HCSCI admitted to the pulmonary rehabilitation center and receiving the center's standard treatment were retrospectively reviewed, focusing on respiratory state transitions.
RESULTS: In total, 133 individuals with a C1–4 neurological level of injury (A: 101 or B: 32 on the American Spinal Injury Association Impairment Scale) were identified; 110 (82.7%) had indwelling tracheostomy tubes at admission and 75 underwent successful decannulation during admission. At the final follow-up, 76 individuals (57.1%) still required mechanical ventilation (MV) and 37 (27.8%) still required indwelling tracheostomy tubes. Of the individuals who had tracheostomy tubes without ventilatory support, 30 underwent decannulation and were discharged without non-invasive MV support. Of those with MV via tracheostomy on admission, 25 were switched to non-invasive MV after decannulation.
CONCLUSION: Respiratory management in complete or sensory incomplete HCSCI needs to be determined by reflecting the current ventilatory state with a comprehensive evaluation of pulmonary function and ventilatory state monitoring. Pulmonary rehabilitation in individuals with HCSCI should be emphasized in the aspect of improving quality of life by avoiding unwanted tracheostomy and changing management methods depending on their recovery.

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INTRODUCTION

Respiratory dysfunction in spinal cord injury (SCI) can lead to respiratory complications, such as reduced vital capacity (VC), impaired secretion clearance, and autonomic dysfunction [1]. Individuals with high cervical SCI (HCSCI) have higher morbidity and mortality due to respiratory complications, resulting in an increased risk of tracheostomy or increased dependency on mechanical ventilation (MV) [2–5]. Pulmonary rehabilitation after SCI with respiratory complications was developed and studied to improve respiratory function recovery in the acute phase and quality of life in the chronic phase. In the first year after the injury, the respiratory function increases as other functions recover [6]. Thereafter, age-related decline occurs faster for those requiring assistance than for those who can live independently or with minimal assistance [7, 8].

Individuals with HCSCI have a higher rate of ventilatory insufficiency than those with lower cervical or thoracic level injuries. Therefore, predicting chronic conditions and providing proper respiratory management based on the SCI status are necessary. Prematurely ceasing MV support aggravated by ventilatory insufficiency results in an unnecessary tracheostomy, which is disadvantageous for the individual. However, proper respiratory care management with effective secretion clearance can prevent ventilatory problems. This study details our experience managing the respiratory recovery of individuals with HCSCI by retrospectively analyzing courses in respiratory management to provide a reference for other pulmonary clinics.

METHODS

Participants

This retrospective study was conducted at the pulmonary rehabilitation center at a tertiary university hospital, where most individuals with HCSCI and ventilatory insufficiency throughout Korea are referred. Individuals with HCSCI admitted to our pulmonary center for pulmonary rehabilitation from January 2011 to December 2020 were recruited; 133 consecutive cases were included. In our institution, pulmonary rehabilitation includes respiratory function assessment, ventilatory support and status monitoring, decannulation or extubation, and daily pulmonary rehabilitation, focusing on non-invasive method. The rehabilitation expert team consists of medical specialists of rehabilitation medicine, physical therapists, pulmonary physiotherapists, occupational therapists, assistant nurse practitioners, and social workers. Individuals who died from unexpected accidents or

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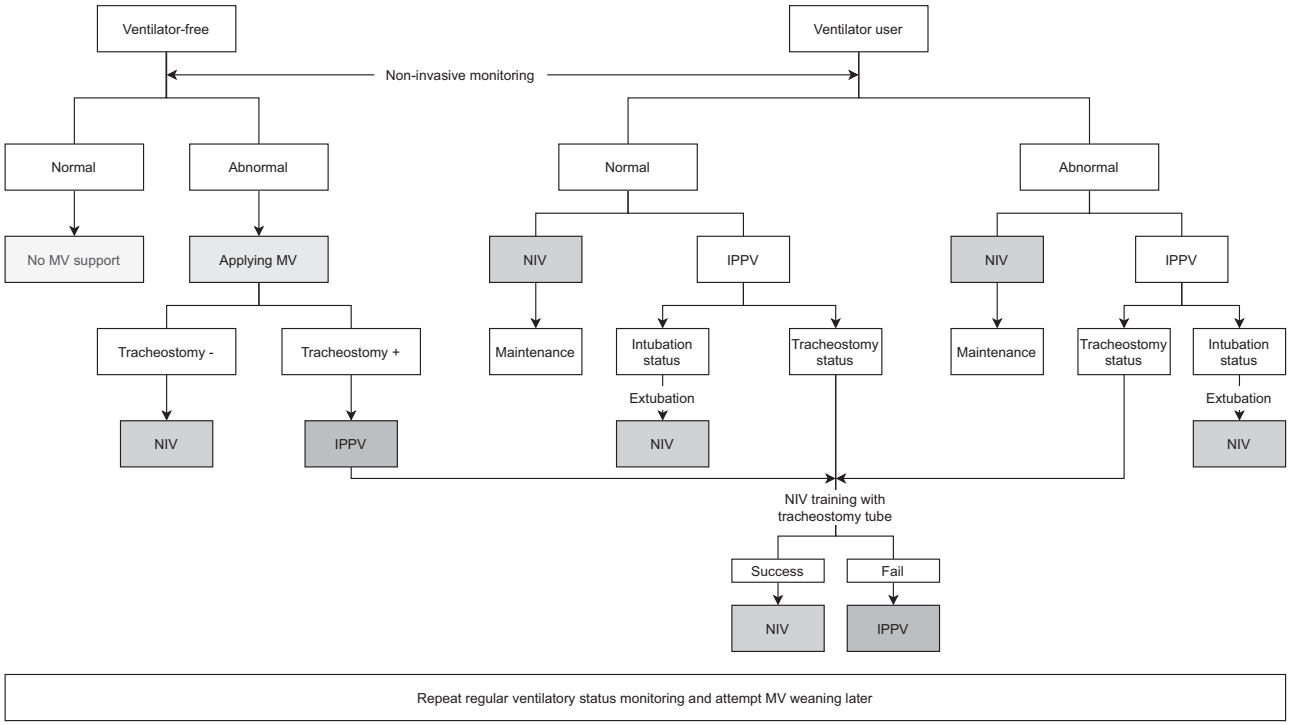

Fig. 1 Flowchart outlining the ventilation support and decannulation process via non-invasive monitoring. MV mechanical ventilation, NIV non-invasive mechanical ventilation, IPPV invasive positive pressure ventilation.

sepsis due to other causes, except pneumonia, were excluded. Individuals refusing any follow-up despite the necessity for further management were also excluded. The medical records were reviewed for discharge notes, imaging studies, and pulmonary function tests, including ventilation monitoring results. Participant demographics (e.g., onset age, duration from the onset, and sex), injury etiology, the grade of American Spinal Injury Association Impairment scale, neurologic level of injury (NLI) classification, and the initial respiratory management status on admission (e.g., tracheostomy, decannulation, or MV) were analyzed. The respiratory care transitions and the final respiratory status after respiratory management were also collected and categorized based on NLI.

Respiratory function assessment and ventilatory status monitoring

The ventilatory status was non-invasively monitored by measuring arterial oxyhemoglobin saturation and carbon dioxide (CO_2) levels by end-tidal CO_2 or transcutaneous CO_2. Arterial oxyhemoglobin saturation was monitored by oximetry (Nellcor™ OxiMax N-560 & Nellcor™ Bedside SpO_2 Patient Monitoring System; Covidien-Medtronic, Minneapolis, MN, USA). End-tidal CO_2 was monitored via capnometry (iMEC10; Mindray, Shenzhen, China or CARESCAPE B450; GE Healthcare, Chicago, IL, USA). Transcutaneous CO_2 was monitored via V-sign™ System (SenTec, Therwil, Switzerland).

To evaluate respiratory muscle strength, pulmonary function was assessed by forced VC in the sitting and supine positions, maximum inspiratory pressure, and maximum expiratory pressure at each admission. Peak cough flow (PCF) was measured by unassisted and assisted coughing. Assisted coughing was measured with maximal insufflation by air stacking with an inflating bag followed by a bimanual abdominal thrust. All measurements were performed by a peak flow meter (ASSESS®; Health Scan Products Inc., Cedar Grove, NJ, USA) with the participant coughing as hard as possible, and the highest value from three or more attempts was recorded.

Choice of respiratory management

The respiratory state was invasively and non-invasively evaluated on admission to the pulmonary rehabilitation center. Ventilation assistance was determined based on the results of 24-h, continuous non-invasive ventilatory monitoring (Fig. 1). Individuals with HCSCI were divided into ventilator-free and ventilator-user groups. Ventilator-free individuals had normal results from the continuous ventilatory monitoring without signs of hypercapnia (partial pressure of $CO_2 > 50$ cm H_2O), consistent desaturation (oxygen saturation <95%), and bulbar dysfunction with aspiration [9]. For these individuals, their ventilatory management did not change. An abnormal ventilatory status with hypercapnia and with or without desaturation indicated that MV was required. If there was only desaturation without hypercapnia, the case was evaluated with uncontrolled secretion or sleep apnea as the cause. The MV type was selected by the presence of a tracheostomy tube. Ventilator-user individuals were assigned to be trained by non-invasive mechanical ventilation (NIV) if the monitoring results were normal. For those with abnormal results, the ventilator setting was readjusted (Fig. 1).

Decannulation and extubation principles for changing the ventilatory support strategy

The decannulation process for individuals with an SCI and tracheostomy is described in the literature [10, 11]. Briefly, individuals should be alert and must not have communication issues. Several conditions must be evaluated for successful decannulation and extubation, such as intrinsic lung diseases, bulbar dysfunctions, airway patency with intact vocal cord mobility, and partial pressure of CO_2 elevation when the oxygen saturation (SaO_2) is ≥95% in ambient air.

Frequent aspiration due to dysphagia can make successful decannulation difficult. Videofluoroscopic swallowing study can assess dysphagia and predict decannulation success. All individuals with SCI with tracheostomy tubes were evaluated for dysphagia to confirm obvious aspiration and penetration. Ear, nose, and throat specialists performed flexible fiberoptic endoscopy to evaluate the airway patency, vocal cord movement issues, tracheal stenosis, granulomatous lesions, or signs of dysphagia. Next, the tracheostomy tube was switched to the cuffless-type tube with an exchangeable fenestrated or non-fenestrated inner cannula. For those meeting the conditions for decannulation, attempts to cap the tracheostomy tube were made. If the individual had continuous tracheostomy mechanical ventilation (TMV), the ventilation setting was returned to NIV via oronasal or nasal interfaces while capping the tracheostomy tube. The initial setting was individually adjusted to maintain normal ventilation status. All individuals were educated on manually assisted coughing as preparation for decannulation. If coughing was not enough to remove a large amount of sputum, mechanical insufflation-exsufflation (CoughAssist; Philips-Respironics International Inc., Murrysville, PA, USA) was used to assist oral self-expectoration.

Individuals with tracheostomy underwent videofluoroscopic swallowing study to confirm signs of aspiration, especially in the liquid phase. If the individual had clinical symptoms with liquid aspiration, such as a wet voice after a meal or desaturation despite using mechanical insufflation-exsufflation, the tracheostomy tube could not be removed. The physician proceeded with decannulation and extubation based on strict criteria after confirming the continuous monitoring results [10, 11]. Individuals were weaned from ventilatory support by gradually lowering assisted insufflations based on daily ventilation monitoring results while maintaining normal SaO_2 and normal CO_2 levels [12].

RESULTS

Demographic characteristics

In total, 133 individuals with motor complete HCSCI receiving pulmonary rehabilitation were included (Table 1). The mean (SD) onset age was 50.8 (15.9) years. The number of men was 119 (89.5%), which was approximately eight times that of women. More individuals had an American Spinal Injury Association Impairment Scale grade A injury ($n = 101$, 75.9%) than grade B injury. Most individuals were NLI C4, but the proportion decreased as the level of injury increased. Most injuries were due to transport injuries (44.4%), followed by fall injuries (27.1%). Non-traumatic SCI included tuberculous spondylitis, epidural hematoma, cord infarction, and cord tumors (neurofibromatosis, cavernous malformation, hemangioblastoma, and glioblastoma).

Respiratory management at initial admission

On admission or arrival to the pulmonary rehabilitation center, the median duration from the onset was 2 months. Sixty-one individuals (45.9%) were not assisted by MV. Only three individuals (2.3%) had intermittent or continuous NIV via nasal or oronasal masks. Most individuals maintained continuous TMV ($n = 69$, 51.9%) (Table 2).

Final respiratory status at discharge

The final respiratory status had several distinguishable categories, characterized by tracheostomy status and ventilation status. The mean (SD) follow-up duration was 20.5 (35.9) months. Of the 57 individuals with no MV support, only 5 maintained indwelling tracheostomy tubes at the final follow-up. Two individuals had CO_2 retention without ventilation assistance on admission. One of those maintained NIV, and the other was weaned off the MV after training with NIV. While 69 individuals were TMV-assisted at initial admission, only 32 (24.0%) maintained TMV at the last discharge (Table 3). Of the individuals with a tracheostomy, 75 were decannulated, and 14 were successfully weaned off the MV.

Table 1. Participant demographics ($n = 133$).

Characteristics	Number of participants
Onset age (years), mean (SD)	50.8 (15.9)
Sex (M:F)	119:14
Neurological level (*n*)	
C1	6 (4.5%)
C2	24 (18.0%)
C3	42 (31.6%)
C4	61 (45.9%)
ASIA impairment scale (*n*)	
A	101 (75.9%)
B	32 (24.1%)
Etiologies of injury	
Sports	22 (16.5%)
Assault	4 (3.0%)
Transport	59 (44.4%)
Fall	36 (27.1%)
Other traumatic cause	4 (3.0%)
Non-traumatic cause	8 (6.0%)

ASIA American Spinal Injury Association.

Table 2. The respiratory management status at the initial admission ($n = 133$).

Status	Number of participants
Mean duration from onset, months (SD)	11.2 (28.8)
Maximum duration from onset (months)	202
Categories	
No MV	61 (45.9%)
Without tracheostomy	18 (13.5%)
With tracheostomy	43 (32.3%)
MV support	72 (54.1%)
Maintaining NIV	3 (2.3%)
Maintaining TMV	69 (51.9%)

MV mechanical ventilation, *NIV* non-invasive mechanical ventilation, *TMV* tracheostomy mechanical ventilation.

Table 3. The final respiratory status at the last discharge ($n = 133$).

Status	Number of participants
Mean follow-up duration, months (SD)	20.5 (35.9)
Maximum follow-up duration (months)	223
Categories	
No MV	57 (42.9%)
Without tracheostomy	52 (39.1%)
With tracheostomy	5 (3.8%)
MV support	76 (57.1%)
NIV	44 (33.1%)
TMV	32 (24.0%)

MV mechanical ventilation, *NIV* non-invasive mechanical ventilation, *TMV* tracheostomy mechanical ventilation.

Initial to final respiratory state transitions

Figure 2 presents the overall respiratory state transitions; 18 individuals did not depend on MV or undergo tracheostomy. The respiratory status of 11 individuals among the group without MV support at initial admission did not differ at the last discharge, but the others had a status change due to abnormal respiratory status results at admission. Of the individuals admitted after tracheostomy but without MV, 30 underwent decannulation during admission. They were discharged without NIV. Conversely, nine underwent decannulation but needed to use NIV intermittently. For individuals who started NIV, it was maintained and finely adjusted using the ventilator settings. Of those who received TMV at admission, 53 individuals remained on invasive or non-invasive MV, three were weaned off TMV without decannulation, and 25 transitioned to NIV after decannulation upon discharge. In two cases, the individuals underwent intubation upon admission, which was immediately after acute injuries. One of these individuals was successfully extubated using NIV and pulmonary rehabilitation physicians as a backup, but extubation failed for the other due to their medically unstable condition (variceal bleeding and septic shock with a multi-drug-resistant bacterial infection).

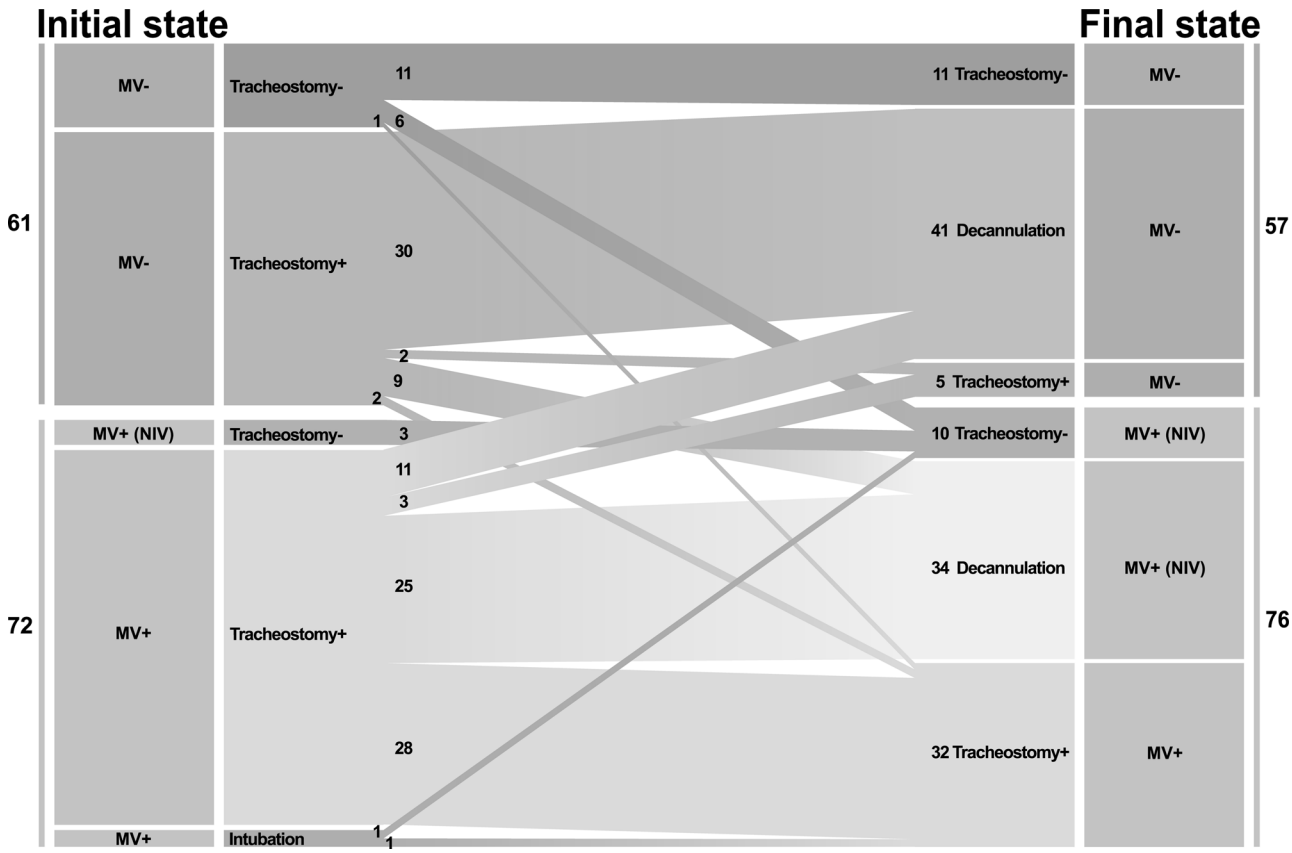

Fig. 2 Initial to final respiratory state transitions. MV mechanical ventilation, NIV non-invasive mechanical ventilation.

While the majority of the 80 individuals who tried decannulation underwent successful decannulation, there were 5 individuals who failed decannulation and kept the tracheostomy tubes at the last discharge. One individual with an NLI C4 injury was not given ventilatory support. However, the individual eventually underwent tracheostomy during admission. In this case, extubation had been performed at another hospital and was not on MV before admission. There, the individual was discovered to have pneumonia and subsequently intubated after admission under invasive positive pressure ventilation support. After recovered from pneumonia, extubation was attempted by management in the intensive care unit. Despite NIV support, atelectasis and a large amount of secretion were unresolved. Consequently, tracheostomy was performed, and TMV was applied 24 h a day. There was a readmission loss and revisits to outpatient clinics after discharge.

Decannulation failed in four others despite the lack of requirement for MV. All four had an NLI C4 injury and were transferred to the hospital after tracheostomy at other institutions. At the final follow-up, one individual maintained the tracheostomy with TMV 24 h a day after cardiopulmonary resuscitation due to accidental tube blockage by a burst tube balloon. Another individual using continuous positive airway pressure was admitted while capping the tracheostomy tube but changed to TMV due to increased oxygen demand. This individual tried weaning and decannulation on the second and third admissions. However, the tracheostomy tube could not be removed due to capping difficulties with persistent dyspnea. Another individual underwent re-tracheostomy due to the repeated regrowth of granulation tissue despite successful decannulation after granulation tissue removal surgery. The last individual had a continuous silent aspiration of small liquid, such as saliva, despite being ventilator-free. Thus, the tracheostomy tube was kept without considering decannulation. This individual was likely to have decannulation after their next visit. However, subsequent visits were lost to follow-up.

Of the individuals who used MV and had tracheostomy tubes, three were successfully weaned, all of which had an NLI C4 injury. Although VC and PCF were not measurable, weaning was successful after their pneumonia improved without CO_2 retention in room air. However, the tracheostomy was kept due to persistent small liquid aspiration or dyspnea while capping the tracheostomy tube. At the final follow-up, 28 individuals remained on MV and had very low (unmeasurable) VC and PCF, and most had small liquid aspiration. Three individuals continued to attempt tracheostomy tube capping due to reduced NIV compliance and were lost to follow-up after being transferred to another hospital.

Finally, two individuals were intubated and started with invasive positive pressure ventilation support at the initial admission, and a tracheostomy was performed after extubation failure for one individual with an NLI C2 injury. After re-hospitalization, their MV-free status was checked daily. However, it was decided to continue TMV due to recurrent pneumonia.

DISCUSSION

HCSCI is similar to other SCIs in that the prognosis for chronic conditions differs by neurological injury level. Selecting the most suitable respiratory management via regular ventilatory monitoring based on the individual's condition is crucial for improving their quality of life.

For individuals with HCSCI, tracheostomy is often performed soon after the injury owing to the high probability of respiratory

failure [13, 14]. A previous study reported that 98.1% of individuals with HCSCI underwent tracheostomy [14]. However, our study indicates that the respiratory function of individuals with HCSCI can improve without reluctant tracheostomy if NIV training was used simultaneously based on the individual's changing respiratory status. With the development of pulmonary rehabilitation and the evolution of portable mechanical ventilators, NIV frees some individuals with respiratory failure after extubation from undergoing tracheostomy [11].

An individual's final respiratory state was classified by their level of injury to confirm management changes. Overall, NLI C4 was the most common ($n = 19$) in simple decannulation. Of NIV users with decannulation, NLI C3 was the most common ($n = 14$), and of TMV users, NLI C2 was the most common ($n = 21$). The number of individuals with NLI C1 was too small. It is inevitable that individuals with a complete cervical level of injury, especially at or above the C3-5 levels, require MV [15]. These types of injuries also lead to respiratory insufficiency and increase pulmonary complications without appropriate management, such as an impaired ability to cough or clear secretions or difficulty swallowing [16]. Over 5 weeks from the onset of injury, the VC gradually increases, almost doubling the initial VC after 3 months [17]. Considering this, even if an individual with a cervical SCI depends on MV at the first hospitalization, the respiratory function should recover enough to eliminate reliance on MV as their neurological function improves.

Motor complete HCSCI had a high dependence on MV. The proportions of MV in this study seem to be similar at the initial admission and the last discharge. However, the characteristic features of respiratory management changed with the individual's respiratory status. For example, MV use changed when individuals without MV required NIV based on initial admission monitoring or when NIV was needed after decannulation during hospitalization at the pulmonary rehabilitation center. MV reliance decreased when the respiratory management changed from continuous TMV to intermittent TMV, TMV to NIV, or when an individual was completely weaned from MV.

Although most individuals with SCI are intubated and undergo tracheostomy to secure a definite airway during the acute period of the initial injury, respiratory management may change as the pulmonary function improves and the NLI recovers. In our study, we compared the conditions at the initial admission and the last discharge of individuals with HCSCI and the high demand for ventilator support. This study aimed to report changes and characteristics of respiratory management performed at our pulmonary rehabilitation center. MV was applied in individuals with respiratory insufficiency if extubation and decannulation were conducted without proper monitoring. Reducing MV dependence was possible for individuals with sufficiently recovered respiratory function. This study also confirmed that a transition from TMV to NIV may be needed in some individuals requiring respiratory assistance but had improved dysphagia or that complete MV weaning is possible under consecutive monitoring. Some physicians are wary of such attempts in individuals with HCSCI due to difficulties accessing MV and interpreting indirect monitoring tools. As demonstrated in this study, if MV is applied together with respiratory state changes and physicians gain clinical experience, such difficulties can be overcome.

This was a retrospective cohort study with inherent limitations. To analyze the respiratory management in a chronic state, respiratory function and the management state should be measured for at least 1 year after onset when NLI no longer changes [18]. In this study, there were only 19 individuals for whom more than 1 year had elapsed from the onset, but the statistical analyses remain possible if there are more eligible participants. Furthermore, although our center deals with extensive nationwide data, this is a single institutional study. Since the total number is small, additional studies based on multi-centers are necessary. It is possible to statistically analyze the difference in the characteristics and prognosis of respiratory management in non-traumatic and traumatic SCI. The data presented in this study focused on the pattern of change based on the respiratory function and management state when the individuals were hospitalized and discharged at our center. If the data directly describe the initial vector and status at the time of injury, then prognoses correlating with the initial function can be analyzed in SCI.

In conclusion, the proper respiratory management for individuals with motor complete HCSCI may be confirmed by examining the pulmonary function and assessing ventilatory state monitoring. The goal of pulmonary rehabilitation in these patients is to increase their quality of life by eliminating unnecessary tracheostomies and adapting their care to reduce their reliance on MV based on their recovery.

DATA AVAILABILITY

The datasets generated and analyzed in this study are available from the corresponding author on reasonable request.

REFERENCES

1. Berlly M, Shem K. Respiratory management during the first five days after spinal cord injury. J Spinal Cord Med. 2007;30:309–18.
2. Jackson AB, Groomes TE. Incidence of respiratory complications following spinal cord injury. Arch Phys Med Rehabil. 1994;75:270–5.
3. DeVivo MJ, Krause JS, Lammertse DP. Recent trends in mortality and causes of death among persons with spinal cord injury. Arch Phys Med Rehabilitation. 1999;80:1411–9.
4. Fishburn MJ, Marino RJ, Ditunno JF Jr. Atelectasis and pneumonia in acute spinal cord injury. Arch Phys Med Rehabil. 1990;71:197–200.
5. Reines HD, Harris RC. Pulmonary complications of acute spinal cord injuries. Neurosurgery. 1987;21:193–6.
6. Haisma JA, Bussmann JB, Stain HJ, Sluis TA, Bergen MP, Dallmeijer AJ, et al. Changes in physical capacity during and after inpatient rehabilitation in subjects with a spinal cord injury. Arch Phys Med Rehabilitation. 2006;87:741–8.
7. Jain NB, Brown R, Tun CG, Gagnon D, Garshick E. Determinants of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC in chronic spinal cord injury. Arch Phys Med Rehabilitation. 2006;87:1327–33.
8. Shavelle RM, DeVivo MJ, Strauss DJ, Paculdo DR, Lammertse DP, Day SM. Long-term survival of persons ventilator dependent after spinal cord injury. J Spinal Cord Med. 2006;29:511–9.
9. Bach JR. Noninvasive respiratory management of high level spinal cord injury. J Spinal Cord Med. 2012;35:72–80.
10. Bach JR, Saporito LR, Shah HR, Sinquee D. Decanulation of patients with severe respiratory muscle insufficiency: efficacy of mechanical insufflation-exsufflation. J Rehabil Med. 2014;46:1037–41.
11. Kim DH, Kang SW, Choi WA, Oh HJ. Successful tracheostomy decannulation after complete or sensory incomplete cervical spinal cord injury. Spinal Cord. 2017;55:601–5.
12. Bach JR, Saporito LRJC. Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure: a different approach to weaning. Chest. 1996;110:1566–71.
13. Harrop JS, Sharan AD, Scheid EH Jr., Vaccaro AR, Przybylski GJ. Tracheostomy placement in patients with complete cervical spinal cord injuries: American Spinal Injury Association Grade A. J Neurosurg. 2004;100:20–3.
14. Branco BC, Plurad D, Green DJ, Inaba K, Lam L, Cestero R, et al. Incidence and clinical predictors for tracheostomy after cervical spinal cord injury: a National Trauma Databank review. J Trauma. 2011;70:111–5.
15. Brown R, DiMarco AF, Hoit JD, Garshick E. Respiratory dysfunction and management in spinal cord injury. Respir Care. 2006;51:853–68.
16. McMichan JC, Michel L, Westbrook PR. Pulmonary dysfunction following traumatic quadriplegia. Recognition, prevention, and treatment. JAMA. 1980;243:528–31.
17. Ledsome JR, Sharp JM. Pulmonary function in acute cervical cord injury. Am Rev Respir Dis. 1981;124:41–4.
18. Spiess MR, Muller RM, Rupp R, Schuld C, EM-SCI Study Group, van Hedel HJ. Conversion in ASIA impairment scale during the first year after traumatic spinal cord injury. J Neurotrauma. 2009;26:2027–36.

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AUTHOR CONTRIBUTIONS

JP and S-WK designed and wrote the study protocol and submitted the study to the ethical committee. JP also wrote the report, collected and analyzed data, and interpreted the results. WAC assisted with the protocol design and recruited and managed participants. S-WK contributed insights regarding the results and provided feedback on the manuscript. S-WK confirms the full access to the study data and has final responsibility for the decision to submit for publication.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

This study was approved by the Institutional Review Board of Gangnam Severance Hospital (No. 3-2020-0229).

ADDITIONAL INFORMATION

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