Respiratory Complications of Spinal Cord Injury

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Impairments in respiration resulting from spinal cord injury (SCI) result in medical consequences that are leading causes of morbidity, mortality, and economic burden. Pulmonary complications of SCI include increased risk of pulmonary infection and death, and higher rates of symptoms of respiratory dysfunction. Inspiratory capacity is diminished in individuals with higher level lesions, contributing to microatelectasis, dyspnea with exertion, and, in those with more severe impairments, respiratory insufficiency. Muscles of expiration are impaired in many individuals with spinal cord injury (eg, injury >T8) with profound effects on cough effectiveness and, presumably, on clearance of secretions and susceptibility to lower respiratory tract infections. In persons with SCI, quality of life is diminished by respiratory symptoms that include cough, phlegm, and wheezing (1,2). In those with higher lesions, asthma-like disorders of airway function have been described, which are prevented by cholinergic antagonists. This abnormality has been attributed to the unopposed effects of parasympathetic innervation on respiratory smooth muscle resulting from disruption of sympathetic efferents (3). Hope for reductions in the impact of these many respiratory complications comes from new technologies that support respiration, continued growth of knowledge about the specific characteristics and impact of the respiratory complications of SCI, and interventions to reduce their severity. From a more fundamental viewpoint, gains in function of respiratory musculature after SCI, whether occurring spontaneously or stimulated by rehabilitation paradigms, point to the plasticity of the nervous system and its ability to form new connections after SCI.

In this issue of the *Journal of Spinal Cord Medicine* are 7 articles about aspects of respiratory complications of SCI, which provide a perspective of current knowledge about respiratory complications and progress toward current treatments and prevention. Four research articles provide new information about the nature of these complications, the technologies to relieve them, and the neurobiology by which new connections formed within the spinal cord may limit them.

Smith and coworkers report on visit rates for respiratory complications based upon analysis of administrative data for more than 18,000 veterans with SCI over a 5-year period. Although the findings of this study are limited by missing information on the level and completeness of injury and, potentially, on visits to non-VA healthcare providers for respiratory symptoms, it has unique strengths including the large number of subjects and availability of comparable data for able-bodied veterans. In agreement with two smaller prospective studies, the authors reported a positive relationship between level and completeness of injury. Risks of pneumonia were increased 2-fold as compared with able-bodied veterans. A significant number of visits were for influenza, raising an intriguing question as to how the rising rates of influenza vaccination in veterans with SCI will affect this respiratory complication. Additionally, smoking has been shown to adversely affect lung function in persons with SCI (4) raising questions regarding risks of respiratory illness posed by tobacco use for individuals with SCI.

Neuroprostheses employing functional electrical stimulation carry the potential to improve cough and ventilation. Phrenic nerve pacing provides at least partial ventilator independence for some individuals with higher lesions. Technologies that improve cough or ventilation would be expected to result in further long-term reductions in morbidity due to respiratory complications of SCI. Progress toward this goal will require development of electrodes; control systems for arrays of multiple electrodes to intercostal muscles, abdominal muscles, or both; and an understanding of which muscles of respiration must be stimulated and when. In this issue, Walters and coworkers have demonstrated the feasibility of using microstimulators for activation of abdominal and intercostal muscles and the diaphragm. On the one hand, this finding might be expected to expand the repertoire of devices available for the design of future neuroprostheses to support respiration and cough. However, as acknowledged by the authors, much work remains to be done before microstimulators become standard tools for implementation of neuroprostheses in this setting.

In mammals, hemisection of the cervical spinal cord has been observed to be followed by spontaneous recovery of contraction of the ipsilateral diaphragm resulting from crossover of motor pathways to activate the phrenic nucleus ipsilateral to the hemisection

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(crossed phrenic pathway). Work in this field represents an intriguing intersection of the fields of SCI research, respiratory physiology, and the neurobiology of neuroplasticity. Recruitment of this pathway requires specific adaptations within the spinal cord. Insights into the molecular basis for these adaptations are provided by two studies in this issue of the *Journal*. Evidence that upregulation of the NR2A subunit of the NMDA receptor stimulates such neuroplasticity comes from studies by Alilain and Goshgarian demonstrating that upregulation of this subunit facilitates recovery of motor activity of the ipsilateral phrenic nerve. Petrov and coworkers have explored the molecular basis for findings that adenosine-receptor agonists such as theophylline accelerate ipsilateral phrenic nerve activity. These authors suggest that this effect of theophylline results from preserving normal expression of the A1-adenosine receptor subtype in phrenic nerve motor neurons. Unfortunately, as noted by Zimmer in this issue, damage to the cervical spinal cord in humans with SCI may be too extensive to expect to see the crossed phrenic pathway.

Current knowledge regarding treatment of respiratory complications of SCI is reviewed by Berly and Shem and by Zimmer and coworkers. What is clear from this work is that much progress has been made in developing supportive care to minimize the impact of respiratory complications over the first days or weeks after injury. Morbidity and mortality due to pulmonary infection have proved to be more challenging problems to address. In this regard, one intervention with proven efficacy in other populations is vaccination against influenza virus and *Streptococcus pneumoniae*. Despite the progress in immunizing persons with SCI against influenza, approximately one third to one half (depending on age,

smoking history, and other factors) are not vaccinated even with intensive vaccination paradigms (5). The findings of Trautner and coworkers reported in this issue indicate that one rational way to improve patient acceptance is administration to insensate regions. Individuals with SCI have benefited from advances in pulmonary research; however, progress has been slow toward reducing the impact of chronic impairments in cough; symptoms of cough, wheeze, phlegm, and dyspnea; and ventilatory impairments in persons with higher lesions. Areas where rigorous study is needed to develop evidence of efficacy and establish treatment guidelines include presence or absence of benefit for respiratory muscle strength training, cough-assistive devices, and noninvasive ventilation.

REFERENCES

1. Jain NB, Sullivan M, Kazis LE, Tun CG, Garshick E. Factors associated with health-related quality of life in chronic spinal cord injury. *Am J Phys Med Rehabil*. 2007;86:387–396.
2. Spungen AM, Grimm DR, Lesser M, Bauman WA, Almenoff PL. Self-reported prevalence of pulmonary symptoms in subjects with spinal cord injury. *Spinal Cord*. 1997;35:652–657.
3. Grimm DR, Arias E, Lesser M, Bauman WA, Almenoff PL. Airway hyperresponsiveness to ultrasonically nebulized distilled water in subjects with tetraplegia. *J Appl Physiol*. 1999;86:1165–1169.
4. Almenoff PL, Spungen AM, Lesser M, Bauman WA. Pulmonary function survey in spinal cord injury: influences of smoking and level and completeness of injury. *Lung*. 1995; 173:297–306.
5. Weaver FM, Smith B, LaVela C et al. Interventions to increase influenza vaccination rates in veterans with spinal cord injuries and disorders. *J Spinal Cord Med*. 2007;30:10–19.