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Tetraplegia is associated with enhanced peripheral chemoreflex sensitivity and ventilatory long-term facilitation

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Abstract

Cardiorespiratory plasticity induced by acute intermittent hypoxia (AIH) may contribute to recovery following spinal cord injury (SCI). We hypothesized that patients with cervical SCI would demonstrate higher minute ventilation (V_E) following AIH compared with subjects with thoracic SCI and able-bodied subjects who served as controls. Twenty-four volunteers (8 with cervical SCI, 8 with thoracic SCI, and 8 able-bodied) underwent an AIH protocol during wakefulness. Each subject experienced 15 episodes of isocapnic hypoxia using mixed gases of 100% nitrogen (N_2), 8% O_2 , and 40% CO_2 to achieve oxygen saturation 90% followed by room air (RA). Measurements were obtained before, during, and 40 min after AIH to obtain ventilation and heart rate variability data [R-R interval (RRI) and low-frequency/ high-frequency power (LF/HF)]. AIH results were compared with those of sham studies conducted in RA during the same time period. Individuals with cervical SCI had higher V_E after AIH compared with able-bodied controls ($117.9 \pm 23.2\%$ vs. $97.9 \pm 11.2\%$, $P < 0.05$). RRI decreased during hypoxia in all individuals (those with cervical SCI, from $1,009.3 \pm 65.0$ ms to 750.2 ± 65.0 ms; those with thoracic SCI, from 945.2 ± 65.0 ms to 674.9 ± 65.0 ms; and those who were able-bodied, from 949 ± 75.0 to 682.2 ± 69.5 ms; $P < 0.05$). LF/HF increased during recovery in individuals with thoracic SCI and those who were able-bodied (0.54 ± 0.22 vs. 1.34 ± 0.22 and 0.67 ± 0.23 vs. 1.82 ± 0.23 , respectively; $P < 0.05$) but remained unchanged in the group with cervical SCI. Our conclusion is that patients with cervical SCI demonstrate ventilatory long-term facilitation following AIH compared with able-bodied controls. Heart rate responses to hypoxia are acutely present in patients with cervical SCI but are absent during posthypoxic recovery.

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AUTHOR CONTRIBUTIONS

A.S. and M.S.B. conception and design of research; A.T.B. performed experiments; A.T.B. and A.R. analyzed data; A.S. and M.S.B. interpreted results of experiments; A.S. prepared figures; A.S. drafted manuscript; A.S. and M.S.B. edited and revised manuscript; A.S. and M.S.B. approved final version of manuscript.

DISCLOSURES

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Keywords

hypoxia; long-term facilitation; acute intermittent hypoxia; plasticity; cardiac autonomic response; spinal cord injury

Spinal cord injury (SCI) is the second most common cause of paralysis, affecting more than one million individuals in the United States alone (44). Unfortunately, life expectancy in patients with SCI remains less than the general population, despite improved critical care, targeted rehabilitation, and longer short-term survival (53). Cardiac and respiratory disorders are the two leading causes of morbidity and mortality in patients with SCI (18). In fact, patients with SCI experience repetitive episodes of hypoxia during sleep due to impaired cough, decreased lung volume, impaired chest wall mechanics (16, 49), and higher prevalence of sleep-disordered breathing (SDB) than the general population (47, 48, 52). The ensuing, intermittent hypoxia can induce sensory long-term facilitation (LTF), which manifests by increased peripheral chemo-responsiveness, enhanced LTF following acute intermittent hypoxia (AIH) (41), and increased propensity to central apnea in a similar fashion to that of patients with obstructive sleep apnea (11).

Intermittent hypoxia-induced neural plasticity may play an important role in motor and sensory recovery following SCI (39). Likewise, cardiac and respiratory plasticity induced by AIH may contribute to respiratory recovery following SCI. Tester et al. (56) demonstrated ventilatory LTF in patients with SCI under hypercapnic conditions. However, the presence of hypercapnia during the recovery period may have amplified the ventilatory response. Furthermore, the study did not assess the effect of SCI level on the magnitude of ventilatory LTF, nor did it assess the associated cardiac responses to hypoxia. The purpose of this study was to determine whether LTF evoked by AIH is dependent on the level of SCI and is coupled by cardiac autonomic modulations. Patients with tetraplegia are at risk for developing hypocapnic apneic threshold, indicating increased breathing instability, compared with individuals with thoracic SCI and those who are able-bodied (48). We hypothesized that patients with cervical SCI would demonstrate higher $\dot{V}_E$ following AIH compared with individuals with thoracic SCI and subjects who served as able-bodied controls. Results of this study have been previously reported in the form of abstracts (8).

METHODS

The Human Investigation Committee of the Wayne State University and the John D. Dingell VA Medical Center approved the experimental protocol. Informed written consent was obtained from all participating subjects. We studied three groups of adults: those who were able-bodied, and those with cervical (C4–C7) SCI and thoracic (T1–T6) SCI (more than 1 yr after injury) with American Spinal Injury Association (ASIA) scores A, B, C, or D.

Each subject was connected to a breathing circuit with a nasal mask attached to a pneumotachometer (model 3700A; Hans Rudolph, Shawnee, KS) to measure ventilation and timing. End-tidal carbon dioxide (P_{ETCO_2}) and O_2 (P_{ETO_2}) were measured with CO_2 and O_2 gas analyzers (models 17515 and 17518, respectively; VacuMed, Ventura, CA) and acquired by a PowerLab data acquisition system (model 16SP, AD Instruments, Colorado Springs,

CO). Standard electroencephalography and electrocardiography readings were recorded using a Comet PSG System (Grass Technologies, Warwick, RI). For baseline overnight sleep tests, attended full-polysomnography (PSG) were obtained from all subjects with cervical and thoracic SCI using Comet or Grass Heritage II (Grass Technologies) systems. Four able-bodied control subjects underwent unattended full PSG using a Compumedics Somte PSG System (Compumedics, Charlotte, NC). Arterial O₂ saturation (SaO₂) was measured by a pulse oximeter using an ear probe (Biox 3740; Datex-Ohmeda, Madison, WI).

Acute Intermittent Hypoxia Protocol

All participants underwent AIH and sham protocols during wakefulness in the supine position on two different occasions during the daytime. Each subject underwent 15 episodes of hypoxia (1 min duration) followed by exposure (2-3 min) to room air (RA) as depicted in Figures 1A and 2A. Three cylinders containing 100% nitrogen (N₂), 8% oxygen (O₂), and 40% CO₂ were connected to the inspiratory circuit through a gas blender (model PMR4, Orangeburg, NY). Isocapnia was maintained throughout the study by bleeding CO₂ (40% gas tank, balanced with N₂) into the circuit and manually adjusting the flow at the blender as hypoxia was induced to prevent hypocapnia. During this procedure, P_{ET}CO₂ was measured continuously, and the CO₂ flow was adjusted to maintain P_{ET}CO₂ near its baseline level. In the sham protocols, subjects breathed RA for the same duration of time that elapsed as during the AIH protocols. If breathing was unstable before beginning an AIH protocol, CO₂ gas was added to the inspiratory circuit and flow was titrated at the blender until breathing stabilized. This titrated flow of CO₂ was then maintained for the entire study in both AIH and sham protocols.

Peripheral Chemoreceptor Activity Protocol

To determine the relative contribution of the peripheral chemoreceptors to eupnic ventilation, all participants underwent brief exposure to hyperoxia during wakefulness in the supine position before the AIH protocol. Each subject underwent three episodes of hyperoxia (1 min duration) followed by exposure to RA (2 to 3 min) as depicted in Figure 3. High-flow 100% O₂ was connected to the inspiratory circuit through a gas blender (model PMR4).

Data Analysis

Ventilatory measurements—Measurements were obtained on a breath-by-breath basis during baseline (1-min segment before first hypoxia) and recovery (measured at 20 [R20], 25 [R25], 30 [R30], and 40 min [R40], respectively) for tidal volume (V_T) and V_E. AIH results were compared with those of sham studies that were conducted in RA over the same period without AIH. The hypoxic ventilatory response (HVR) was measured from the AIH periods and was defined as the change in V_E for a corresponding change in SaO₂ ($\Delta V_E / \Delta \text{SaO}_2$) during the AIH trials.

To assess progressive augmentation in response to AIH, the first and last three hypoxia episodes were compared for each subject. LTF was defined as the percent change in V_E during the recovery period compared with baseline. Breath-to-breath variability was measured using coefficients of variation for V_E (CV-V_E) at baseline

and recovery periods in all subjects during AIH and sham protocols. For hyperoxia experiments, the ventilatory response to hyperoxia was defined as the $\dot{V}_E$ (nadir breath) following the acute hyperoxia exposure compared with the preceding baseline (10 breaths).

Heart rate variability measurements—The heart rate (HR) and ECG measurements were obtained throughout the study for both AIH and sham protocols. Measurements were obtained on a beat-by-beat basis during baseline and recovery for RRI and HR variability (HRV) using spectral power analysis. Specifically, HRV spectral analysis was performed using a fast Fourier transform size of 1,024, and a Welch window. HRV spectral analysis was employed in 2-min stable wake segments during baseline and recovery for each subject. Normalized low-frequency power (nLF), normalized high-frequency power (nHF), and the low-frequency power to high-frequency power ratio (LF/HF) were determined. To assess immediate cardiac responses to AIH, HR and RRI were also measured during each AIH episode at baseline, at the nadir SaO_2 and following AIH termination as depicted in Figs. 1B and 2B.

Statistical Analysis

One-way ANOVA tests were used to compare all demographic variables, baseline characteristics, ventilatory and HR data, and mean HVR. Two-way repeated-measures ANOVA was used to compare $\dot{V}_E$ normalized to baseline between R20 and R40 in the three groups (cervical SCI vs. thoracic SCI vs. able-bodied control subjects). A one-way ANOVA was used to compare $\dot{V}_T$ and breathing frequency (F_B) in the three groups (cervical SCI vs. thoracic SCI vs. able-bodied control subjects) in each AIH and sham protocol. Two-way repeated-measures ANOVA was used to compare CV- $\dot{V}_E$ between baseline and recovery for AIH and sham protocols. Analysis included $n = 8/\text{group}$ for AIH studies, and for sham studies data from three subjects were removed (two subjects with cervical SCI and one able-bodied control individual) due to technical problems. Two-way repeated-measures ANOVA was used to compare the mean HRV (LF, HF, and LH/HF) at baseline and recovery periods between the three groups and between AIH and sham protocols. The Student-Newman-Keuls test was used for all post hoc pairwise multiple comparisons. To ascertain potential determinants of the LTF in all three groups, a Spearman's correlation test was used to assess the relationship between $\dot{V}_E$ (% of baseline) and the following variables: age, body mass index (BMI), and apnea hypopnea index (AHI). A multiple linear regression analysis was used to ascertain potential determinants of ventilatory LTF using the correlating variables described above and level of SCI (level 1, able-bodied; level 2, thoracic SCI; level 3, cervical SCI). All analyses were performed using SigmaStat software (v.12.5; Systat Software, Richmond, CA). A value of $P < 0.05$ was considered significant.

RESULTS

We studied 24 human subjects (8 in each group) during wakefulness in the supine position. All subjects completed both AIH and sham protocols (although the sham protocol was excluded in two subjects with cervical SCI and one able-bodied subject due to technical problems). The three groups had similar demographics; the main difference was a higher AHI and oxygen desaturation index in individuals with cervical SCI compared with those

with thoracic SCI (Table 1). The majority of subjects with spinal injury (6 of 8 with cervical SCI and all subjects with thoracic SCI) were classified as A on the ASIA impairment scale. The remaining subjects were classified C or D (both with cervical SCI). There was no difference in ventilatory baseline parameters among the three groups (Table 2). RA ventilation occurred for 2–3 min between hypoxia episodes to achieve a complete return to normoxia in all subjects, especially those who had unstable breathing. The average time between hypoxia trials and RA ventilation was similar among the three groups (cervical SCI, 2.2 ± 0.5 min; thoracic SCI, 2.6 ± 0.9 min; able-bodied controls, 2.3 ± 0.3 min; $P = 0.63$). The majority of the AIH and sham studies (71%) were performed during a similar time of the day (within 1 h).

Ventilatory Responses to Acute Hyperoxia and Hypoxia

Compared with able-bodied subjects and those with thoracic SCI, subjects with cervical SCI experienced a significant decrease in $\dot{V}_E$ (compared with baseline values) within the first 20 s of hyperoxia (mean F_{iO_2} 70%) as depicted in the representative polygraph (Fig. 3). Figure 4, A and B, shows the summary data for the ventilatory responses to acute hyperoxia and hypoxia, respectively, among the three groups. Note that after hyperoxia, $\dot{V}_E$ decreased significantly in individuals with cervical SCI compared with able-bodied control subjects and those with thoracic SCI ($P < 0.05$).

Although there was no significant difference in HVR among three groups, HVR in subjects with cervical SCI and thoracic SCI was higher than it was in able-bodied control subjects ($P = 0.08$). When data were combined from both groups of individuals with cervical and thoracic SCI, the HVR was significantly higher than it was in able-bodied individuals ($P = 0.02$). Furthermore, there was no significant difference in HVR between the initial (first three) and final (last three) hypoxia episodes in any group as depicted in Figure 5 ($P = 0.48$).

Effect of AIH on ventilation—Exposure to hypoxia was associated with similar degrees of oxyhemoglobin desaturation and a similar increase in $\dot{V}_E$ ($P < 0.05$) (Table 2). The addition of supplemental CO_2 maintained isocapnia or mild hypercapnia during the hypoxic periods ($P < 0.05$). Termination of hypoxia was associated with persistent hyperpnea in subjects with cervical SCI, but not in able-bodied individuals or those with thoracic SCI. Figure 6 depicts the changes in $\dot{V}_E$ during the posthypoxic recovery period. $\dot{V}_E$ during the recovery period (between R20 and R40) was higher than baseline control levels in individuals with cervical SCI ($P < 0.05$), but not in individuals with thoracic SCI ($P = 0.09$) or able-bodied participants ($P = 0.16$). Increased $\dot{V}_E$ in participants with cervical SCI was due to increased V_T to $126.3 \pm 22.3\%$ of baseline ($P < 0.05$) without corresponding changes in respiratory frequency ($P = 0.30$; Fig. 7, A and B). However, increased V_T in the recovery period was noted in both groups of individuals with SCI ($P < 0.05$), but it was higher in individuals with cervical SCI compared with those with thoracic SCI ($P < 0.05$). There was no increase in V_T in the able-bodied group. There was no hyperpnea in the corresponding recovery period during the sham study (Fig. 7, C and D). Specifically, $\dot{V}_E$ in the sham protocol during the recovery period was $91.5 \pm 8.2\%$ of baseline in individuals with cervical SCI compared with $98.0 \pm 9.6\%$ in individuals with thoracic SCI ($P = 0.55$) and $93.5 \pm 9.6\%$ in able-bodied individuals ($P = 0.72$). The ventilatory variability for $\dot{V}_E$ (CV- $\dot{V}_E$) during AIH

studies was significantly higher in individuals with cervical SCI than in able-bodied control individuals and those with thoracic SCI, both at baseline and recovery ($P < 0.05$). Following AIH, individuals with thoracic SCI exhibited an increase in $CV-V_E$ during recovery periods compared with baseline values ($P < 0.05$). $CV-V_E$, however, did not change either in individuals with cervical SCI ($P = 0.14$) nor those who were able-bodied ($P = 0.20$) (Fig. 8A). On the other hand, there was a significant increase in $CV-V_E$ in individuals with cervical SCI during the sham protocol compared with able-bodied individuals ($P < 0.05$), but there was not a significant difference in $CV-V_E$ between those with thoracic SCI and cervical SCI ($P = 0.05$) or between those with thoracic SCI and able-bodied individuals ($P = 0.12$) (Fig. 8B). There also was no significant increase in $CV-V_E$ during the recovery following the sham protocol compared with baseline values ($P = 0.17$).

Determinants of posthypoxic ventilation—To ascertain potential determinants of V_E in the recovery period, we used a Spearman's correlation analysis ($n = 24$). This analysis revealed that V_E in the recovery period correlated with BMI ($R = -0.54$, $P = 0.006$), level of injury ($R = 0.62$, $P = 0.001$), and age ($R = 0.52$, $P = 0.009$) but did not correlate with AHI ($P = 0.18$). Using multiple linear regression models, the linear combination of SCI level ($P = 0.007$) and BMI ($P = 0.006$) predicted ventilatory LTF. For each level increase (able-bodied control > thoracic SCI > cervical SCI) in the group, posthypoxia recovery V_E increased 10% from baseline. Moreover, in a subset of subjects matched for AHI and other demographic characteristics (Table 3), V_E and V_T remained higher in individuals with cervical SCI than in the other two groups during recovery.

Effect of AIH on HRV—Figure 9A illustrates the group changes in HR before, during, and after each hypoxia episode. Note that baseline RRIs were similar between able-bodied individuals and those with cervical SCI ($P = 0.77$). Hypoxia was associated with decreased RRI ($74.3 \pm 5.7\%$, $71.4 \pm 12.1\%$ and $71.8 \pm 13.2\%$ baseline in cervical SCI, thoracic SCI, and able-bodied groups, respectively; $P < 0.05$). Compared with baseline values, nLF and LH/HF during the recovery period did not increase in individuals with cervical SCI, contrary to that in the groups of able-bodied individuals and those with thoracic SCI as shown in Fig. 9B ($P < 0.05$).

DISCUSSION

Our study demonstrated the following novel and significant findings regarding the effects of AIH on the respiratory and cardiac systems both in able-bodied subjects and those with chronic SCI: 1) subjects with chronic SCI experience a significant increase in V_E and V_T (compared with prehypoxia base-line levels) during the recovery phase after AIH. The increased V_T was most prominent in participants with cervical SCI, less prominent in those with thoracic SCI, and absent in able-bodied subjects. 2) Hyperoxia was associated with decreased V_E in individuals with cervical SCI compared with those with thoracic SCI and those who were able-bodied. 3) HVR was similar among the three groups. 4) Subjects with cervical SCI demonstrated a cardiac response to acute hypoxia that was manifested by a decreased RRI similar to that in subjects with thoracic SCI and those who were able-bodied. 5) Heart rate variability, specifically nLH and the LH/HF ratio, did not change significantly

in subjects with cervical SCI during the recovery period after AIH in contrast to able-bodied subjects and those with thoracic SCI.

Methodological Considerations

Several considerations may influence the interpretation of the findings in this study. First, ventilatory changes in the recovery period could not be due to time-related ventilatory changes, given the lack of change in $\dot{V}_E$ and $\dot{V}_T$ during the sham studies. Second, differences in the magnitude of LTF could not be explained by differences in gender distribution or the different prevalence of SDB among the three groups. Previous studies in a rat model showed that there are sex differences in phrenic LTF following C2 hemisection (15). Studies in humans, however, have demonstrated no gender difference in LTF (1, 2, 54). Likewise, LTF following AIH is less pronounced in patients with sleep apnea relative to non-apneic patients (1). Moreover, when we compared a subset of subjects from each group, matching for AHI, those with cervical SCI had higher $\dot{V}_E$ than able-bodied subjects and those with thoracic SCI. Therefore, robust LTF in the group with cervical SCI was due to the cervical spine injury per se and not to the underlying SDB. Third, ventilatory variability measured by $CV-\dot{V}_E$ increased in subjects with cervical SCI from baseline to recovery in AIH protocols but not the sham protocols, indicating that the increased $CV-\dot{V}_E$ is likely due to intermittent hypoxia. Fourth, we were unable to obtain power frequency (nLH and nHF) during brief hypoxia periods because this type of analysis requires longer duration than our brief hypoxic periods. To mitigate this limitation, we measured R-R intervals during hypoxia and the frequency component of the HRV during baseline and recovery periods in all subjects. Finally, our experimental paradigm was limited to wakefulness, and we are unable to draw firm conclusions regarding LTF during sleep in patients with SCI.

Long-Term Facilitation in Chronic SCI

The major finding of our study was that AIH resulted in hyperpnea during the recovery period in individuals with SCI, but not in able-bodied individuals despite similar respiratory parameters at baseline (Table 2). Ventilatory LTF manifested by increased $\dot{V}_T$ and $\dot{V}_E$, without a change in respiratory frequency. This finding corroborates previous studies in awake patients with SCI (56) and in sleeping, able-bodied individuals (2, 41), demonstrating evidence of LTF in the aftermath of repetitive hypoxia. In contrast, the pattern of LTF in humans differs from that in rodent models, which manifests as a significant increase in both frequency and $\dot{V}_T$ after AIH (5), the ventilatory LTF in humans is mainly due to increased $\dot{V}_T$. Increased $\dot{V}_T$ and $\dot{V}_E$ in participants with SCI in our study are suggestive of phrenic LTF.

The lack of ventilatory LTF in able-bodied individuals in this study is in agreement with data from previous studies demonstrating the absence of LTF during wakefulness in healthy humans or during sleep in patients with obstructive sleep apnea (1, 26). LTF during wakefulness in able-bodied humans may require significant hypercapnia (4–6 mmHg greater than baseline levels) that is sustained throughout the hypoxic exposure and the recovery period (24). In contrast, patients with SCI demonstrated ventilatory LTF even under conditions of isocapnia or mild hypercapnia (1–2 mmHg above baseline) during hypoxia trials followed by returning to base-line end-tidal CO_2 levels between hypoxic episodes and

during the recovery phase. It is of note that the addition of supplemental CO₂ alters the relationship between arterial and end-tidal P_{CO₂}, resulting in a slightly negative PaCO₂-P_{ETCO₂} difference of 1.0 to 1.5 mmHg and an underestimation of PaCO₂ during the hypoxic episodes (4). Thus our hypoxic episodes were either isocapnic or slightly hypercapnia. Therefore, the propensity to develop LTF following AIH was enhanced in patients with SCI and did not require hypercapnia. Another important observation in this study was the increased V_T during recovery after AIH in the group of individuals with cervical SCI compared with able-bodied subjects and those with thoracic SCI (Fig. 7A). This increase in tidal volume during recovery in individuals with cervical SCI compared with those with thoracic SCI suggests that the activation of LTF in humans with SCI could be dependent on the level of injury.

Our study corroborates the findings of Tester et al. (56) who demonstrated, using an AIH protocol, that ventilatory LTF is acutely increased in patients with SCI during wakefulness when end-tidal CO₂ remained elevated during recovery. Our study showed, however, that LTF was elicited during RA recovery even in the absence of sustained hypercapnia during the posthypoxic (RA) recovery period, and that the degree of ventilatory LTF was related to the level of SCI (more in cervical SCI than in thoracic SCI).

Several factors may influence the presence of ventilatory plasticity, including arousal state, age, gender, and the presence of SDB. Although it has been shown in animal models that age and gender may affect phrenic LTF (14, 59), human studies did not show gender-related differences in ventilatory LTF (52). SDB may influence the magnitude of LTF in humans during wakefulness and sleep, as has been shown previously in non-injured subjects (1, 2, 51), but not in SCI as we observed in our study. When a subset of subjects matched for AHI and other demographics were compared, ventilatory LTF remained higher in patients with cervical SCI than in able-bodied individuals or those with thoracic SCI (Table 3).

The precise mechanisms responsible for ventilatory LTF in individuals with chronic SCI are unknown. We considered several possible mechanisms on the basis of available literature, mainly performed in animal models of SCI, including central (supraspinal), spinal, or peripheral mechanisms. First, activation of LTF is a serotonin-dependent central nervous system (CNS) phenomenon most likely acting via the serotonin 2A receptor on phrenic motor neurons (27, 35, 37). The neuroplastic changes in respiratory motor output after SCI in animal models coincides with the spontaneous recovery of phrenic function, some of which is modulated by serotonin-containing neurons (19). Chemo-afferent neuron activation during hypoxia results in serotonin receptor activation, which is necessary to initiate phrenic LTF but not to maintain it (17). Second, SCI may be associated with enhanced LTF due to mechanisms that are similar to those triggered by cervical dorsal rhizotomy in the absence of a direct contusion of the spinal cord. Evidence from animal studies has indicated that SCI may cause interruption of the raphe-spinal pathway and lead to a reduction in spinal serotonin content (35). AIH can induce the release of serotonin in rodent models following cervical SCI (3, 20). Moreover, cervical spinal deafferentation enhances phrenic LTF after intermittent hypoxia by increasing brain-derived neurotrophic factor and neurotrophin-3 protein concentrations within neurons of the ventral spinal cord, augmenting the descending serotonergic pathways from the raphe nuclei to the spinal dorsal horn and increasing the

serotonin terminal density near phrenic motor neurons (27). Furthermore, it has been reported that exposure to intermittent hypoxia evokes short-term potentiation of phrenic motor neuron discharge after chronic cervical SCI in animal models (14, 29). Accordingly, enhanced LTF in patients with SCI, especially cervical SCI, could be explained by injury-related spinal respiratory motor plasticity. Finally, LTF following AIH may also be explained by increased afferent chemo-transmission from the carotid bodies to the raphe nuclei resulting in an increased density of serotonergic neurons and hence the intensity of LTF (42). The increased peripheral chemoreceptor contribution to eupnic ventilation, as evidenced by the augmented response to hyperoxia in patients with SCI is consistent with the hypothesis that augmented LTF in patients with SCI, especially in those with cervical SCI, was due to increased afferent activity from the peripheral chemoreceptors. The dynamic interaction between peripheral and central chemoreceptors in humans may contribute to ventilatory changes and unstable breathing under conditions of hypoxia (13). The development of LTF may reflect an augmentation of the magnitude of activation of sensory LTF by chronic intermittent hypoxia. However, the lack of difference in HVR among individuals in the three groups is inconsistent with sensory LTF playing a significant role.

In summary, LTF is a central neural mechanism elicited by intermittent but not continuous hypoxia (5). The occurrence of LTF in laboratory models requires spinal serotonin receptor activation and spinal protein synthesis (6). LTF in patients with SCI could be due to cervical spinal deafferentation or to prior conditioning with chronic intermittent hypoxia (17, 21). Our data do not permit us to distinguish between these broad possibilities in a given individual. However, it is clear that the net effect of level of injury, CNS adaptive changes, and chronic intermittent hypoxia produce a robust LTF in cervical SCI, which could manifest even during wakefulness.

Effect of Acute Intermittent Hypoxia on the Cardiac Autonomic System

We found that HR increased significantly in response to acute hypoxia in all three groups (those with cervical SCI or thoracic SCI, and able-bodied individuals), indicating preserved sympathetic excitatory input to the heart. Our study demonstrated that acute cardiac response to hypoxic stimulation was preserved in patients with cervical SCI and was similar to that of able-bodied individuals (25% increase in HR in response to 10% drop in SaO₂). It has been reported previously that the sympathetic cardiac activity is reduced or absent in humans with SCI (22, 28, 56) and in rats after spinal cord transection (29, 57). Other investigators reported some activity related to sympathetic spinal interneurons in the absence of supraspinal brainstem control (10). The majority of our subjects were classified A on the ASIA impairment scale and had similar reflexes to those of able-bodied controls in their HR response to acute hypoxia. Our finding is consistent with the observation that in animal models, there is significant plasticity after SCI that could explain the observed cardiac reflexes (32, 33, 34).

Our study demonstrated marked differences among the three groups in the response to nLF and LF/HF ratio, surrogate markers of sympathetic and sympathovagal balance, respectively. We observed a significant increase in nLF HRV and LF/HF ratio during RA

recovery in able-bodied individuals and those with thoracic SCI but not in those with cervical SCI. Increased sympathetic cardiac response to hypoxia during recovery in able-bodied individuals and those with thoracic SCI are indicative of persistent long-term sympathetic activation following chemical stimulation. Our finding corroborates a previous study in humans showing that brief hypoxia resulted in “long-lasting sympathetic activation” during recovery (40). The lack of persistent elevation in sympathetic outflow during RA recovery in cervical SCI suggests that the sympathovagal balance is impaired. SCI can lead to an autonomic imbalance between the sympathetic and parasympathetic outflow to the heart predominantly due to loss of supraspinal sympathetic control after cervical SCI (25). Therefore, the cardiac autonomic alterations depend on the level of injury, and the severity is dependent on the relative loss of supraspinal control of the afferent inputs (23, 56).

Effect of Acute Intermittent Hypoxia on the Cardiac and Respiratory Systems

The major finding of our study was that AIH resulted in increased ventilation coupled with increased HR in individuals with SCI, even after termination of hypoxia. Our study also demonstrated that cervical SCI is associated with loss of LH, HF, or LH/HF response following AIH. Control of cardiorespiratory responses occurs on the ventrolateral surface of the medulla, which integrates afferent inputs from central and peripheral receptors, controls the excitatory inputs to preganglionic sympathetic neurons in the spinal cord, and coordinates the primary interactions between neurons responsible for generating the respiratory rhythm and determining HRV (38). Different disturbances such as hypoxia and arousals that commonly occur in patients with SDB affect the afferent rather than the efferent control of respiratory and cardiac systems via sympathetic nerve activity (SNA) (23). Furthermore, there is evidence that SNA modulates the respiratory responses even after vagotomy and decerebration, indicating a role for central coupling between respiratory and sympathetic networks (7). This coupling seems to be an important mechanism of immediately increasing ventilation and cardiac output reflexes to allow for better tissue oxygenation and appropriate cardiovascular and respiratory responses to maintain homeostasis. The dissociation between cardiac and ventilatory responses following intermittent hypoxia in patients with cervical SCI suggests that there are different or redundant pathways for cardiac and ventilatory plasticity.

Clinical Implications

The occurrence of ventilatory LTF in patients with SCI highlights the role of neuroplasticity in ventilatory recovery following SCI and the possible additive contribution of the level of injury and underlying SDB. Accordingly, respiratory plasticity following repetitive intermittent hypoxia may be more pronounced in patients with cervical SCI than thoracic SCI or in able-bodied individuals. Second, the enhanced respiratory output in cervical SCI in response to AIH indicates a potential therapeutic target for patients who experience hypoventilation, particularly during sleep. Conceptually, using a serotonin agonist may facilitate ventilatory recovery without the deleterious effects associated with chronic intermittent hypoxia. Finally, the cardiorespiratory modulations in cervical SCI could help identify the neural pathway and allow differentiation between peripheral vs. central mechanisms of intermittent hypoxia. Thus cervical SCI could represent a potential clinical model representing a mechanism of plasticity common to other neural systems in humans.

In summary, we have shown the occurrence of ventilatory LTF induced by intermittent isocapnic hypoxia in chronic SCI. Ventilatory LTF is primarily dependent on the level of SCI. The cardiac responses to acute hypoxia stimuli are preserved in cervical SCI without significant long-term alterations in HRV during recovery.

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Fig. 1.

A representative polygraph recording of intermittent hypoxia protocol from an able-bodied control subject that illustrates respiratory changes (*A*) and heart rate changes (*B*) using R-R interval before, during, and 40 min after acute intermittent hypoxia (AIH).

Fig. 2.

A representative polygraph recording of intermittent hypoxia protocol in a subject with cervical spinal cord injury (SCI) that illustrates respiratory changes (A) and heart rate changes (B) using R-R interval before, during, and 40 min after AIH during recovery while breathing room air.

Fig. 3.

A representative polygraph recording of the hyperoxia protocol from a subject with cervical SCI that illustrates ventilatory changes in room air and during hyperoxia (1 min).

Fig. 4.

A: summary data to illustrate ventilatory response to hyperoxia ($\text{HO-}\dot{V}_E$) presented as (%) a change in minute ventilation ($\dot{V}_E$) from baseline in able-bodied subjects ($n = 8$) and those with cervical SCI ($n = 8$) or thoracic SCI ($n = 8$). *B*: hypoxic ventilatory response (HVR) during hypoxia episodes in groups of able-bodied individuals ($n = 8$) and those with cervical SCI ($n = 7$) or thoracic SCI ($n = 8$). Note that $\text{HO-}\dot{V}_E$ decreased significantly in the group of individuals with cervical SCI compared with baseline. *Cervical SCI vs. able-bodied controls (one-way, repeated-measures ANOVA and Student-Newman-Keuls post hoc significance $P < 0.05$).

Fig. 5.

Summary data to illustrate hypoxic ventilatory response (HVR) during early (black bars) and late (white bars) AIH episodes in groups of able-bodied individuals ($n = 8$) and those with cervical SCI ($n = 8$) or thoracic SCI ($n = 8$). Two-way repeated-measures ANOVA, Student-Newman-Keuls post hoc test.

Fig. 6. Minute ventilation (V_E) changes during recovery from acute intermittent hypoxia at 20 min (R20) through 40 min (R40) in groups of able-bodied individuals ($n = 8$) and those with cervical SCI ($n = 8$) or thoracic SCI ($n = 8$). *Cervical SCI vs. able-bodied controls (two-way repeated-measures ANOVA and Student-Newman-Keuls post hoc significance $P < 0.05$).

Fig. 7.

Ventilatory changes presented as the average (%) change from baseline in tidal volume (V_T) (A) and frequency (F_B) (B) during the period between 20 and 40 min of recovery after acute intermittent hypoxia (AIH) in three groups of individuals: able-bodied, and those with cervical SCI or thoracic SCI. Ventilatory changes from baseline are presented as means $\pm$ SE for V_T (C) and F_B (D) during the sham protocol. For AIH studies, $n = 8/\text{group}$ except for sham studies where $n = 6$ for the cervical SCI group and $n = 7$ for the able-bodied group. +Vs. able-bodied controls, *vs. thoracic SCI group (one-way ANOVA and Student-Newman-Keuls post hoc significance $P < 0.05$).

Fig. 8.

Ventilatory coefficient of variation (CV-V_E) presented as % change in variation for V_E during baseline control (black bars) and recovery (white bars) following acute intermittent hypoxia (A) and sham (B) protocols in three groups of able-bodied control subjects and those with cervical SCI or thoracic SCI. Data are means $\pm$ SE, $n = 8$ /group for AIH studies except for sham studies for which $n = 6$ for the cervical SCI group and $n = 7$ for the able-bodied group. *Vs. baseline, ‡vs. thoracic SCI, †vs. able-bodied (two-way repeated measures ANOVA and Student-Newman-Keuls post hoc significance $P < 0.05$).

Fig. 9.

Cardiac changes in R-R interval (RRI) and heart rate variability. *A*: RRI at baseline (black bars), during hypoxia (white bars), and during posthypoxia (gray bars) in able-bodied individuals and those with cervical SCI or thoracic SCI. *B*: heart rate variability changes using power frequency analysis presented as the low-frequency-power to high-frequency-power ratio (LF/HF) for baseline while breathing room air (black bars) and during recovery while breathing room air (gray bars) in the three groups. *Vs. baseline, +vs. baseline, ‡vs. cervical SCI (two-way repeated measures ANOVA and Student-Newman-Keuls post hoc significance $P < 0.05$).

Table 1

Subjects characteristics

	Cervical SCI	Thoracic SCI	Able-bodied
Number	8	8	8
Age, yr	44.3 ± 15.1	37.0 ± 14.9	35.5 ± 18.1
BMI, kg/m ²	25.6 ± 4.9	26.9 ± 5.4	26.9 ± 4.1
Gender, M/F	7/1	4/4	5/3
NC, cm	39.1 ± 2.9	37.2 ± 3.1	35.5 ± 4.0
Time since SCI, yr	11.8 ± 6.5	13.9 ± 6.1	—
AHI, event/h	30.7 ± 18.6*	10.4 ± 10.5	5.5 ± 3.7
ODI, event/h	20.4 ± 19.2*	5.5 ± 12.1	1.2 ± 1.0

AHI, apnea-hypopnea index; BMI, body mass index; NC, neck circumference; ODI, Oxygen desaturation index; SCI, spinal cord injury. Data are means ± SD.

* Cervical SCI vs. able-bodied controls, one-way ANOVA $P < 0.05$.

Table 2

Ventilatory parameters at baseline and acute hypoxia

	Cervical SCI		Thoracic SCI		Able-bodied	
	Baseline	Hypoxia	Baseline	Hypoxia	Baseline	Hypoxia
$\dot{V}_E$, liter/min	7.4 ± 2.3	16.0 ± 7.4 *	6.7 ± 1.9	16.6 ± 4.1 *	8.7 ± 1.9	13.6 ± 1.9 *
V_T , liter	0.5 ± 0.2	1.0 ± 0.3 *	0.4 ± 0.1	0.9 ± 0.2 *	0.5 ± 0.1	0.9 ± 0.3 *
f_B , breaths/min	14.5 ± 2.3	15.2 ± 3.1	15.5 ± 2.9	18.6 ± 3.5	19.2 ± 4.9	17.5 ± 4.9
T_I , s	1.9 ± 0.3	2.0 ± 0.4	1.8 ± 0.4	1.5 ± 0.3	1.5 ± 0.4	1.8 ± 0.8
T_E , s	2.4 ± 0.6	2.2 ± 0.6	2.2 ± 0.4	1.9 ± 0.3	1.9 ± 0.4	2.1 ± 0.7
$P_{ET}CO_2$, mmHg	40.3 ± 4.5	42.5 ± 4.1 *	39.6 ± 2.3	41.0 ± 3.0 *	36.6 ± 3.3	37.8 ± 3.8
S_aO_2 , %	96.8 ± 1.3	84.9 ± 2.2 *	96.7 ± 2.4	86.1 ± 1.3 *	97.3 ± 1.5	85.9 ± 1.1 *

$\dot{V}_E$, minute ventilation; V_T , tidal volume; f_B , breathing frequency; T_I , inspiratory time; T_E , expiratory time; $P_{ET}CO_2$, end-tidal CO_2 ; S_aO_2 , oxygen saturation. Data are means ± SD.

* Baseline vs. hypoxia, two-way repeated-measures ANOVA and Student-Newman-Keuls post hoc significance, $P < 0.05$.

Table 3

Results of ventilation change during recovery in a subset of matched subjects for AHI and respective characteristics

Subject	SCI status	V _T , %	V _E , %	Age, yr	BMI, kg/m ²	Gender	NC, cm	AHI, event/h
1	SCI-C	156.7	123.5	56	25.6	F	34.5	9.3
2	SCI-C	153.8	134.5	33	19.3	M	39.0	11.7
3	SCI-T	118.5	96.8	28	30.2	M	43.5	10.3
4	SCI-T	107.3	103.5	71	35.0	F	38.0	9.9
5	Able	83.5	84.9	70	30.3	M	39.0	9.7
6	Able	103.2	89.4	23	30.1	M	41.0	4.1

AHI, apnea-hypopnea index; BMI, body mass index; NC, neck circumference; V_E, minute ventilation; V_T, tidal volume (% of baseline).