Inosine: a novel treatment for urologic complications of spinal cord injury

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Harvard Medical School

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Disclosures

Rosalyn M. Adam, PhD has no interest to disclose.

PESG and PVA staff have no interest to disclose.

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. Discuss the urinary tract complications of spinal cord injury and current unmet needs.
2. Describe preclinical evidence for inosine as a novel intervention to improve bladder control following SCI.
3. Discuss potential clinical implementation of inosine in the setting of neurogenic detrusor overactivity.
Urinary tract complications of spinal cord injury

- Loss of normal bladder control - NDO
- Detrusor-sphincter dyssynergia
- Increased risk of autonomic dysreflexia with cervical and thoracic lesions
- Psychological distress, debilitation and social isolation
Urinary tract complications of SCI
Current management

• Catheterization to promote emptying
  – Requires adequate dexterity

• Medication to reduce overactivity
  – Anti-muscarinic receptor blockade
  – Inhibition of neurotransmitter release – botulinum toxin
  – Use of β3 adrenergic receptor agonists

• Durability, adverse effects can be limiting
Inosine

- naturally occurring purine nucleoside
- neurotrophic, neuroprotective, antioxidant
Inosine and SCI

- Stimulates neurite outgrowth in vitro

Inosine promotes motor recovery in vivo

Model system

• Traumatic thoracic SCI in rats (T8)
  – Transection
  – Compression

• Daily systemic administration of inosine for 6 wk
  – Immediate (at time of injury) - prevention
  – Delayed (at 8 wk after injury) - intervention
Model system

- Conscious cystometry
  - Bladder pressure
  - Overactivity
- Contractility testing
  - Muscle function
- Evaluation of neuronal markers
  - Innervation
Bladder wall remodeling with SCI
Functional evaluation - urodynamics
Chronic inosine administration attenuates detrusor overactivity
Inosine decreases frequency and amplitude of non-voiding contractions
Chronic inosine treatment does not alter evoked bladder contractility.
Development of NDO

C-fibers – normally silent, become active following SCI

De Groat et al., (2015)
Compr. Physiol 5: 327-96.
Inosine is neuroprotective
Inosine attenuates TRPV1 levels

Transsection

Vehicle

Inosine

TRPV1 immunoreactivity/mm²

<table>
<thead>
<tr>
<th></th>
<th>Veh</th>
<th>Ino</th>
<th>Veh</th>
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<th>Veh</th>
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<td>2000</td>
<td>1000</td>
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<td></td>
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</tr>
</tbody>
</table>
Summary - I

• Significant reduction in detrusor overactivity
  – Reduced frequency and amplitude of SNVCs
• No apparent effect on evoked muscle contractility
• Alterations in sensory neurotransmission
  – Prevents loss of general neuronal markers
  – Attenuates pathologic upregulation of TRPV1
    • Implicated in development of DO following SCI
RESEARCH ARTICLE

Inosine Improves Neurogenic Detrusor Overactivity following Spinal Cord Injury

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\* \texttt{msullivan@rics.bwh.harvard.edu} (MPS); \texttt{rosalyn.adam@childrens.harvard.edu} (RMA)
Acute intravesical inosine attenuates detrusor overactivity

SNVC Frequency

*\(p=0.015\)

SNVC Amplitude

*\(p=0.0463\)
Modulation of spontaneous activity in vitro

**Graphs A and B**

- **Graph A**
  - Force (g) vs. Time (s)
  - Lines represent Control, Transection, and Clip conditions

- **Graph B**
  - Force (g) vs. Time (s)
  - Key points: Amplitude of low frequency SA, Amplitude of high frequency SA
Inosine reduces spontaneous activity in vitro
Inosine acts via adenosine receptors

Pan-adenosine receptor antagonist: CGS 15943
Inosine acts via $A_2$ receptors, primarily $A_{2B}$.

$A_{2A}$ antagonist: ZM241385

$A_{2B}$ antagonist: PSB603

$A_{2B}$ agonist: BAY 60-6583
BK channels mediate the inhibitory effect of inosine on SA

**SK3 antagonist: Apamin**

**K\textsubscript{ATP} antagonist: Repaglinide**

**BK antagonist: iberiotoxin**

![Graphs showing amplitude changes with different antagonists]
Summary - II

• Inosine elicits profound improvements in neurogenic detrusor overactivity.
• Inosine is effective in prevention and intervention regimens.
• Improvements in NDO are evident with both chronic and acute treatment.
• Adenosine receptor $\mathrm{A}_{2B}$ and BK channels are putative effectors of inosine action.
SURE-PD trial (NCT00833690)

• Oral inosine to elevate uric acid levels in the serum and cerebrospinal fluid of Parkinson’s patients
  – Phase II, randomized, double-blind, placebo-controlled, dose-ranging in pts with early PD
  – Placebo vs mild or moderate serum urate elevation (up to 1000 mg, 3 x day) for up to 24 months
  – Primary endpoints – absence of serious adverse effects, absence of required dose reduction, elevation of serum/CSF uric acid
  – SAEs lower in inosine vs placebo group; 95% tolerance at 6 mos; 3 pts displayed kidney stones
Treatment of Multiple Sclerosis using over-the-counter inosine (NCT00067327)

- Inosine to elevate uric acid in relapsing remitting multiple sclerosis
  - Phase II, randomized, double-blind, interventional efficacy trial in pts with RRMS
  - RRMS pts have reduced levels of serum uric acid compared to age-matched controls
  - No study results reported
A Pilot Study of Inosine in ALS (NCT02288091)

Phase I open label safety and tolerability study
Oral administration of up to 3 g inosine per day to elevate uric acid levels
Primary objective – safety and tolerability
Secondary objective – measurement of serum biomarkers of oxidative stress and damage
Conclusions

• Inosine is a naturally occurring substance with multiple beneficial bioactivities
• Inosine elicits significant improvements in neurogenic detrusor overactivity
• Inosine acts in both chronic and acute settings
• Clinical trials for other indications provide proof-of-principle evidence for safe use in humans
Acknowledgements

• Abhishek Seth, MD
• Carlos Estrada, MD
• Maryrose Sullivan, PhD
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• Larry Benowitz, PhD
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• Claire Doyle, PhD
• Bryan Sack, MD
• Mattias Schäfer, MD
• Stefan Lukianov, MS

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– Children’s Urological Foundation
CE/CME Credit

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http://PVA.cds.pesgce.com
Sleep Disordered Breathing in Patients with SCI
“From Bench to Bedside”

Abdulghani Sankari, MD, PhD
Email: asankari@dmc.org
Disclosures

Presenter has no conflict of interest to disclose.

PESG and PVA staff have no interest to disclose.

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. Characteristics of Sleep disordered breathing in SCI
2. Effect of SCI level on ventilation
3. Mechanism of disease and potential therapeutic targets
Sleep Disordered Breathing (SDB)

“Sleep Apnea”

- Chronic condition characterized by repeated episodes of apnea and hypopnea during sleep.
- OSA Syndrome when associated with daytime symptoms (OSAHS)
- Prevalence: **4-28%**, M/F 1:1-3 (estimated ~**20 million Americans**, ~80% are undiagnosed)
  - DM: 50-80%
  - Atrial Fibrillation: 50-70%
  - CHF: 40-50%
  - Stroke: 50-70%
  - CKD: 40-60%
  - SCI: **60-90%**

A. Sankari 2016
# SDB prevalence in chronic SCI

<table>
<thead>
<tr>
<th>Study</th>
<th># patients</th>
<th>Level</th>
<th>SDB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short et al (1992)</td>
<td>22 (20 M)</td>
<td>T10-above</td>
<td>25% (10% central)</td>
</tr>
<tr>
<td>Flavell et al (1992)</td>
<td>10 (10 M)</td>
<td>Cervical</td>
<td>30% O2sat&gt;10% &lt;90%</td>
</tr>
<tr>
<td>Klefbeck et al (1998)</td>
<td>33 (28 M)</td>
<td>Cervical</td>
<td>15% (ODI &gt;4%)+ PB</td>
</tr>
<tr>
<td>Stockhammer (2002)</td>
<td>50 (40 M)</td>
<td>Cervical</td>
<td>48%</td>
</tr>
<tr>
<td>Sankari et al (2014)</td>
<td>26 (16 M)</td>
<td>T6 -above</td>
<td>77% (AHI &gt;5) PSG</td>
</tr>
<tr>
<td>Bauman et al (2015)</td>
<td>81 (75 M)</td>
<td>T6 -above</td>
<td>81% (AHI&gt;5) HSAT</td>
</tr>
</tbody>
</table>
Fig. 2. A representative polygraph from one cervical SCI patient who had spontaneous central apnea and breathing instability associated with fluctuations in PetCO₂ and O₂ saturation during sleep. FiO₂, fractional inspired O₂.
Scope of The Problem

- Acute vs. chronic
- Neuromuscular weakness
- Level of injury
- Co-morbidities
- Medications
- Chronic Intermittent hypoxia
Sleep Disordered Breathing in Chronic Spinal Cord Injury

Abdulghani Sankari, M.D., Ph.D.; Amy Bascom, M.S.; Sowmini Oommen, M.D., Ph.D.; M. Safwan Badr, M.D., M.B.A.
Sleep Research Laboratory, John D. Dingell Veterans Affairs Medical Center, Wayne State University, Detroit, MI

Study Objectives: Spinal cord injury (SCI) is associated with 2.5 times greater prevalence of sleep disordered breathing (SDB) than the general population. The contribution of SCI on sleep and breathing at different levels of injury using two scoring methods has not been assessed. The objectives of this study were to characterize the sleep disturbances in the SCI population and the associated physiological abnormalities using quantitative polysomnography and to determine the contribution of SCI level on the SDB mechanism.

Methods: We studied 26 consecutive patients with SCI (8 females; age 42.5 ± 15.5 years; BMI 25.9 ± 4.9 kg/m²; 15 cervical and 11 thoracic levels) by spirometry, a battery of questionnaires and by attended polysomnography with flow and pharyngeal pressure measurements. Inclusion criteria for SCI: chronic SCI (> 6 months post injury), level T8 and above and not on mechanical ventilation. Ventilation, end-tidal CO₂ (P₄,CO₂), variability in minute ventilation (V₁-CV) and upper airway resistance (Rₚ₉₀) were monitored during wakefulness and NREM sleep in all subjects. Each subject completed brief history and exam, Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Berlin questionnaire (BQ) and fatigue severity scale (FSS). Sleep studies were scored twice, first using standard 2007 American Academy of Sleep Medicine (AASM) criteria and second using new 2012 recommended AASM criteria.

Results: Mean PSQI was increased to 10.3 ± 3.7 in SCI patients and 92% had poor sleep quality. Mean ESS was increased 10.4 ± 4.4 in SCI patients and excessive daytime sleepiness (ESS ≥ 10) was present in 59% of the patients. Daytime fatigue (FSS > 20) was reported in 98% of SCI, while only 46% had high-risk score of SDB on BQ. Forced vital capacity (FVC) in SCI was reduced to 70.5% predicted in supine compared to 78.5% predicted in upright positions (p < 0.05). Likewise forced expiratory volume in first second (FEV₁) was 64.9% predicted in supine compared to 74.7% predicted in upright positions (p < 0.05). Mean AHI in SCI patients was 29.3 ± 25.0 vs. 20.0 ± 22.8 events/h using the new and conventional AASM scoring criteria, respectively (p < 0.001). SCI patients had SDB (AHI > 5 events/h) in 77% of the cases using the new AASM scoring criteria compared to 65% using standard conventional criteria (p < 0.05). In cervical SCI, V₁ decreased from 7.2 ± 1.6 to 5.5 ± 1.3 L/min, whereas P₄,CO₂ and V₁-CV, increased during sleep compared to thoracic SCI.

Conclusion: The majority of SCI survivors have symptomatic SDB and poor sleep that may be missed if not carefully assessed. Decreased V₁ and increased P₄,CO₂ during sleep in patients with cervical SCI relative to thoracic SCI suggests that sleep related hypventilation may contribute to the pathogenesis SDB in patients with chronic cervical SCI.

Keywords: Sleep, spinal cord injury, tetraplegia, central apnea
Citation: Sankari A; Bascom A; Oommen S; Badr MS. Sleep disordered breathing in chronic spinal cord injury. J Clin Sleep Med 2014;10(1):XXX-XXX.
Characteristics of Chronic SCI: Level dependence

Table 3—Characteristics of sleep and polysomnography data

<table>
<thead>
<tr>
<th></th>
<th>Cervical</th>
<th>Thoracic</th>
<th>p value</th>
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<tbody>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST (minutes)</td>
<td>169.8 ± 65.4</td>
<td>153.0 ± 76.2</td>
<td>NS</td>
</tr>
<tr>
<td>Stage N1 (%)</td>
<td>25.1 ± 20.5</td>
<td>25.1 ± 27.3</td>
<td>NS</td>
</tr>
<tr>
<td>Stage N2 (%)</td>
<td>50.8 ± 16.8</td>
<td>46.7 ± 17.8</td>
<td>NS</td>
</tr>
<tr>
<td>Stage N3 (%)</td>
<td>19.8 ± 19.5</td>
<td>22.7 ± 19.7</td>
<td>NS</td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>4.4 ± 5.8</td>
<td>5.6 ± 10.9</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>60.6 ± 12.6</td>
<td>70.9 ± 25.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean AHI (recommended) (event/h)</td>
<td>20.7 ± 18.7</td>
<td>10.9 ± 20.5</td>
<td>NS</td>
</tr>
<tr>
<td>AHI (% &gt; 5 events/h)</td>
<td>93.0 ± 26.0*</td>
<td>55.0 ± 52.0</td>
<td>0.02</td>
</tr>
<tr>
<td>AHI (% &gt; 15 events/h)</td>
<td>80.0 ± 41.0*</td>
<td>27.0 ± 47.0</td>
<td>0.006</td>
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<tr>
<td>ARI (% &gt; 5 events/h)</td>
<td>86.0 ± 36.0</td>
<td>55.0 ± 52.0</td>
<td>NS</td>
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<tr>
<td>ODI (% &gt; 5 events/h)</td>
<td>57.0 ± 51.0</td>
<td>27.0 ± 47.0</td>
<td>NS</td>
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<tr>
<td>CAI (% &gt; 5 events/h)</td>
<td>40.0 ± 51.0</td>
<td>18.0 ± 40.0</td>
<td>NS</td>
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<tr>
<td>OAI (% &gt; 5 events/h)</td>
<td>33.0 ± 49.0</td>
<td>18.0 ± 40.0</td>
<td>NS</td>
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<tr>
<td>CSR (%)</td>
<td>27.0 ± 46.0</td>
<td>9.0 ± 30.0</td>
<td>NS</td>
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<tr>
<td>PB (%)</td>
<td>60.0 ± 51.0</td>
<td>27.0 ± 47.0</td>
<td>NS</td>
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</tbody>
</table>

All data mean ± SD. TST, total sleep time; AHI, apnea-hypopnea index; ODI, oxygen-desaturation index; ARI, respiratory related arousal index; CAI, central apnea index; OAI, obstructive apnea index; CSR, Cheyne-Stokes Respiration; PB, periodic breathing. *p value < 0.05 cervical vs. thoracic.

Table 4—Characteristics of sleep and polysomnography data after excluding patients using opioids

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<tr>
<td>TST (minutes)</td>
<td>161.2 ± 69.9</td>
<td>144.6 ± 82.3</td>
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<tr>
<td>Stage N1 (%)</td>
<td>31.3 ± 22.9</td>
<td>29.2 ± 29.2</td>
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<td>Stage N2 (%)</td>
<td>48.7 ± 16.8</td>
<td>41.8 ± 16.5</td>
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<tr>
<td>Stage N3 (%)</td>
<td>16.0 ± 12.4</td>
<td>23.8 ± 22.1</td>
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<tr>
<td>REM sleep (%)</td>
<td>4.9 ± 5.5</td>
<td>5.1 ± 11.6</td>
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<tr>
<td>Sleep Efficiency (%)</td>
<td>62.5 ± 9.0</td>
<td>77.7 ± 19.9</td>
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<td>AHI (% &gt; 5 events/h)</td>
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<td>50.0</td>
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<tr>
<td>AHI (% &gt; 15 events/h)</td>
<td>78.0*</td>
<td>25.0</td>
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<tr>
<td>Al-res (events/h)</td>
<td>29.4 ± 23.1</td>
<td>15.2 ± 20.1</td>
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<tr>
<td>CAI (% &gt; 5 events/h)</td>
<td>33.0</td>
<td>13.0</td>
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<tr>
<td>OAI (% &gt; 5 events/h)</td>
<td>33.0</td>
<td>25.0</td>
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</tr>
<tr>
<td>CSR (%)</td>
<td>22.0</td>
<td>0.0</td>
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<tr>
<td>PB (%)</td>
<td>56.0</td>
<td>25.0</td>
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</table>

All data mean ± SD. TST, total sleep time; AHI, apnea-hypopnea index; ODI, oxygen-desaturation index; Al-res, respiratory related arousal index; CAI, central apnea index; OAI, obstructive apnea index; CSR, Cheyne-Stokes respiration. *p value < 0.05 cervical vs. thoracic.
36-year-old man w/ chronic cervical SCI (C6, incomplete) during the transition from wake to sleep

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Amy T. Bascom et al. PHY2 2015;3:e12490
Upper airway mechanics in chronic spinal cord injury during sleep

Abdulghani Sankari, Amy T. Bascom, and M. Safwan Badr

Sleep Research Laboratory, John D. Dingell Veterans Affairs Medical Center, Wayne State University School of Medicine, Detroit, Michigan

Submitted 12 February 2014; accepted in final form 16 April 2014

Sankari A, Bascom AT, Badr MS. Upper airway mechanics in chronic spinal cord injury during sleep. J Appl Physiol 116: 1390–1395, 2014. First published April 17, 2014; doi:10.1152/japplphysiol.00139.2014.—Sleep-disordered breathing has been shown to be more prevalent in patients with spinal cord injury (SCI) than the general population. The pathogenesis of increased sleep-disordered breathing in individuals with chronic SCI is unknown. The purpose of this study is to determine whether SCI level affects upper airway (UA) collapsibility and neuromuscular compensatory responses to obstruction. Twenty-four participants (8 cervical SCI, 8 thoracic SCI, and 8 controls) were studied. The ventilation, timing, UA resistance, and pharyngeal collapsibility, defined by critical closing pressure, were determined during non-rapid eye movement sleep. Inspiratory duty cycle and minute ventilation were observed in response to increasing severity of UA obstruction. Compared with controls, both cervical and thoracic SCI participants demonstrated elevated passive critical closing pressure (0.5 ± 2.2 and 0.9 ± 2.7 vs. −2.5 ± 1.0 cmH₂O, respectively; P = 0.01). No difference in UA resistance was observed between groups. Cervical and thoracic SCI individuals exhibited a similar degree of hypoventilation and dose-dependent increase in inspiratory duty cycle in response to UA obstruction. Passive UA collapsibility is increased in both cervical and thoracic SCI compared with control. The neuromuscular compensatory responses to UA obstruction during sleep are preserved in chronic SCI and are independent of the level of injury.

Methods

Subjects

The Human Investigation Committee of Wayne State University and the John D. Dingell Veterans Affairs Medical Center approved the experimental protocol. An informed, written consent was obtained, and participants had a screening polysomnography. We studied adults (>18 yr old) with chronic SCI and able-bodied participants, if they met the inclusion and exclusion criteria. All subjects were instructed not to have alcohol, caffeine products, or sedatives on the day of the study. Zolpidem was administered at standard doses (5–12.5 mg) one time orally 30 min before sleep to mitigate sleep disruption or difficulty sleeping with instrumentation.
Upper airway collapsibility ($P_{\text{Crit}}$) is higher in the SCI subjects (8 C- & 8 T-) than the able-bodied controls (n=8).

*S* = 0.01

Sankari et al JAP 2014
Determinants of central sleep apnea

Isometabolic hyperbolae

CO₂ Reserve

Controller factor (PG)

Plant factor (PG)
Tetraplegia is a risk factor for central sleep apnea

Abdulghani Sankari, Amy T. Bascom, Susmita Chowdhuri, and M. Safwan Badr
Sleep Research Laboratory, John D. Dingell Veterans Affairs Medical Center, Wayne State University, Detroit, Michigan
Submitted 27 June 2013; accepted in final form 8 October 2013

Sankari A, Bascom AT, Chowdhuri S, Badr MS. Tetraplegia is a risk factor for central sleep apnea. J Appl Physiol 116: 345–353, 2014. First published October 10, 2013; doi:10.1152/japplphysiol.00731.2013.—Sleep-disordered breathing (SDB) is highly prevalent in patients with spinal cord injury (SCI); the exact mechanism(s) or the predictors of disease are unknown. We hypothesized that patients with cervical SCI (C-SCI) are more susceptible to central apnea than patients with thoracic SCI (T-SCI) or able-bodied controls. Sixteen patients with chronic SCI, level T6 or above (8 C-SCI, 8 T-SCI; age 42.5 ± 15.5 years; body mass index 25.9 ± 4.9 kg/m²) and 16 matched controls were studied. The hypocapnic apneic threshold and CO₂ reserve were determined using noninvasive ventilation. For participants with spontaneous central apnea, CO₂ was administered until central apnea was abolished, and CO₂ reserve was measured as the difference in end-tidal CO₂ (PTECO₂) before and after. Steady-state plant gain (PG) was calculated from PTECO₂ and V̇E ratio during stable sleep. Controller gain (CG) was defined as the ratio of change in V̇E between control and hypopnea or apnea to the ΔPTECO₂. Central SDB was more common in C-SCI than T-SCI (63% vs. 13%, respectively; P < 0.05). Mean CO₂ reserve for all participants was narrower in C-SCI than in T-SCI or control group (−0.4 ± 2.9 vs. −2.9 ± 3.3 vs. −3.0 ± 1.2 l/min−1·mmHg−1, respectively; P < 0.05). PG was higher in C-SCI than in T-SCI or control groups (10.5 ± 2.4 vs. 5.9 ± 2.4 treatment are unknown (17). Furthermore, there are insufficient and conflicting data on the type of SDB, the predictors of the increased prevalence of SDB, and the relationship between type of SDB and level of injury (16, 17).

We recently found that more than 90% of cervical SCI patients demonstrated SDB, with the majority demonstrating central SDB not explained by daytime hypoventilation, cardiac dysfunction, or use of narcotics (39a, 39). Interestingly, central apnea was the predominant pattern in cervical (C-) SCI patients, whereas obstructive apnea was the predominant pattern in the thoracic (T-) SCI group. This unique observation may have significant implications regarding the mechanism of SDB in SCI patients. Most existing studies classify SDB in cervical SCI under the rubric “obstructive sleep apnea” (OSA), owing to the limitations of diagnostic tools available to SCI patients and the disparity in access to in-lab diagnostic sleep studies for patients with limited mobility. In fact, increased risk for central apnea in patients with cervical SCI was first reported by Severinghaus and Mitchell (41), who coined the term “On-
**PLANT GAIN IS HIGHER** IN C-SCI COMPARED TO T-SCI

**NO SIGNIFICANT CHANGE IN** CONTROLLER GAIN

**CO₂ RESERVE IS NARROWER** IN C-SCI

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<table>
<thead>
<tr>
<th></th>
<th>Cervical</th>
<th>Thoracic</th>
<th>Control</th>
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<tbody>
<tr>
<td>Plan Gain (mmHg/L/min)</td>
<td>![Bar Chart](Cervical Plan Gain)</td>
<td>![Bar Chart](Thoracic Plan Gain)</td>
<td>![Bar Chart](Control Plan Gain)</td>
</tr>
<tr>
<td>Controller Gain (L/min/mmHg)</td>
<td>![Bar Chart](Cervical Controller Gain)</td>
<td>![Bar Chart](Thoracic Controller Gain)</td>
<td>![Bar Chart](Control Controller Gain)</td>
</tr>
<tr>
<td>CO₂ Reserve (mmHg)</td>
<td>![Bar Chart](Cervical CO₂ Reserve)</td>
<td>![Bar Chart](Thoracic CO₂ Reserve)</td>
<td>![Bar Chart](Control CO₂ Reserve)</td>
</tr>
</tbody>
</table>

*Sankari et al JAP 2014*
Example of **lowering plant gain** by shifting the eupneic CO$_2$ to the **steeper** portion of the metabolic hyperbola (X⇒⇒Y).
Tetraplegia is associated with enhanced peripheral chemoreflex sensitivity and ventilatory long-term facilitation

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Sankari A, Bascom AT, Richani A, Badr MS. Tetraplegia is associated with enhanced peripheral chemoreflex sensitivity and ventilatory long-term facilitation. J Appl Physiol 119: 1183–1193, 2015. First published August 13, 2015; doi:10.1152/japplphysiol.00088.2015—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 (N2), 8% \(O_2\), and 40% \(CO_2\) to achieve oxygen saturation \(\leq 90\%\) 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 (LH/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 \((117.9 \pm 23.2\% \text{ vs. } 97.9 \pm 11.2\%, P < 0.05)\). RRI decreased during hypoxia in all individuals (those with cervical SCI, from 1,009.3 ± 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 ms to 682.2 ± 69.5 ms; \(P < 0.05\)). LH/HF increased during recovery in individuals with thoracic SCI and those who were able-bodied \((0.54 \pm 0.22 \text{ vs. } 1.34 \pm 0.22 \text{ and } 0.67 \pm 0.23 \text{ vs. } 1.82 \pm 0.23, \text{ respectively; } P < 0.05)\) but remained unchanged in the group with cervical SCI. Our conclusion is that patients with 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 chemoresponsiveness, 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 hypcapnic 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
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 reco...
Ventilatory changes presented as the average (%) change from baseline in tidal volume (VT) (A) and frequency (FB) (B) during the period between 20 and 40 min of recovery after acute intermittent hypoxia (AIH) in three groups of individuals: able-bodied, and...
Mechanism

Cervical spinal cord

Classification of serotonin receptors

- Selective
  - 5-HT1A agonist
    - Buspirone
  - 5-HT1B and 5-HT1D agonists
    - Triptans
  - 5-HT2 agonist
    - Trazodone
  - 5-HT4 agonist
    - Cisapride

- Non-selective
  - Ergotamine
  - LSD
Drugs Experiments

Role of Enhancing Serotonin Receptors Activity for Sleep Apnea Treatment in Patients With SCI (REST-SCI)
ClinicalTrials.gov Identifier: NCT02458469
SCI

Resp Mus Weakness

Lung Volume

SLEEP

SDB in SCI “The Perfect Storm”

↑ Pain Sensitivity

Opiates

CO₂ Reserve

PG

UA

Collapsibility

Breathing Instability

Cardiac Instability

Apnea/Hypopnea

Arousal

Hypoxia

↑ Hypoxia

Pain Sensitivity
The image contains a diagram illustrating the relationship between various factors in a neurological condition, specifically spinal cord injury (SCI) associated with sleep-disordered breathing (SDB). The diagram highlights the following key points:

- **SCI** (Spinal Cord Injury) is the starting point.
- **Resp Mus Weakness** (Respiratory Muscles Weakness) leads to reduced lung volume.
- Lung volume reduction affects **CO₂ Reserve**.
- **SDB in SCI** is described as "The Perfect Storm." 
- **Mechanical Rx** and **Drugs** are proposed as potential interventions.
- **Arousal** and **Hypoxia** are critical factors in the breathing instability pathway.
- **Breathing Instability** leads to **Apnea/Hypopnea**.
- **Cardiac Instability** is also impacted by the conditions.
- **Pain Sensitivity** and **Opiates** influence the system, with **O₂** potentially affecting pain sensitivity.

The diagram uses arrows to indicate causative relationships and annotations to highlight specific conditions and interventions.
Conclusion

• **SDB** is **level dependent** (more common in cervical SCI and mixed obstructive+central type).
• Upper airway **collapsibility is increased** in SCI.
• Cervical SCI are more **susceptible to central** sleep apnea than thoracic SCI.
• Hypoxia (AIH) enhances **ventilatory plasticity** (LTF) in cervical SCI in contrast to able bodied individuals.
• The unique respiratory plasticity in SCI can be used as a model to assess the mechanism of disease and develop **new targeted therapies**.
Future Goals

• Mechanism and test **new therapeutic targets** using pre-clinical animal models and clinical studies.

• Studying effect of **combined therapy** including: CPAP, day time intermittent hypoxia, night time O2 w/w/o drug therapy in SCI patients.
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