Research Article

Exploring detailed characteristics of autonomic dysreflexia

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Objectives: Identify clinical and pathophysiologic insights into autonomic dysreflexia (AD) in patients with spinal cord injury (SCI).

Study Design: Analysis of prospectively gathered AD dataset.

Setting: Inpatient Veterans Affairs SCI unit.

Participants: 78 male patients with SCI who experienced AD.

Methods: Statistical methods were utilized to identify the frequency of relative bradycardia vs. tachycardia during AD, the effectiveness of supplemental opioids in managing suspected nociceptive pain mediated AD, the effect of chronicity of SCI on response to pharmacological management of AD, and the response to nitroglycerin ointment in suspected bladder related AD.

Results: 445 episodes of AD were analyzed. The frequency of relative bradycardia and tachycardia with AD were 0.3% and 68.0% respectively. The addition of opioids to an antihypertensive medication protocol did not significantly decrease AD episode duration or magnitude of systolic blood pressure (SBP) change. A strongly matched positive linear correlation was identified between the duration of pharmacologically treated AD episodes and chronicity of SCI ($R^2=0.83$). Bladder related AD episodes treated with nitroglycerin ointment had a faster onset of action (10.8 minutes vs. 15.9 minutes), faster time to reach a safe target blood pressure (16.5 minutes vs 20.9 minutes), and greater decrease in SBP (84.3mmHg vs. 68.6mmHg) than non-bladder related episodes ($P=0.19$, 0.23 , and 0.02 respectively).

Conclusions: AD may commonly occur with relative tachycardia. While further investigation is needed on the effects of chronicity of SCI and pharmacologic management, this study raises multiple directions for future research to understand clinical signs and treatment variables of AD following SCI.

Keywords: Spinal cord injury, Autonomic dysreflexia, Nitroglycerin

Introduction

Autonomic dysreflexia (AD) is a well-known complication of spinal cord injury (SCI). Typically, a noxious stimulus below the level of injury triggers this unregulated sympathetic cascade, leading to focal vasoconstriction. Classically, if the neurological level of injury is at or above T6, this vasoconstriction can involve the splanchnic vessels and lead to the progressive hypertension which typifies AD.¹ If this progressive hypertension is not identified and the offending stimulus is not eliminated, blood pressure can continue to climb placing the individual at risk for stroke, retinal detachment, or even death.²

When the body's baroreceptors sense this increase in blood pressure, they increase parasympathetic signaling as a compensatory mechanism. Through this parasympathetic outpouring, individuals can classically experience bradycardia via the vagus nerve and flushing (focal peripheral vasodilation) above the level of injury, along with sympathetically mediated anserine cutis and diaphoresis.³ However, as with many conditions, this classic constellation of symptoms of AD is rarely seen in its entirety in the clinical setting. This ambiguity can lead to confusion as to whether a given event is, in fact, AD. When conservative measures are unable to address the cause, pharmacologic intervention is often required. Unfortunately, there is little guidance to assist in choosing which medication might be the

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most appropriate. As a medical emergency, any clarity around variable presentations, response to medications, or treatment guiding features on presentation of AD has the potential to be of notable clinical benefit.

Using a robust dataset derived from a large number of episodes of AD that occurred in the hospital setting, we sought to determine the incidence of heart rate changes, the effectiveness of opioids on nociceptive pain mediated AD, the role of chronicity of SCI on medication response, and the response to nitroglycerin ointment in episodes of AD which were thought to be bladder mediated.

Methods

A dataset of episodes of AD previously prospectively recorded as part of a study assessing the safety and utility of an AD treatment protocol⁴ was utilized. This parent study involved recording initial, peak, and conclusion vital signs when an AD event was successfully managed. Presumed etiology of AD and medications given with timing to decrease in systolic blood pressure (SBP) 10 mmHg and time to reach the target SBP of below 160 mmHg were also charted. All episodes of AD were recorded on patients as they were treated on an inpatient, Veterans Affairs Hospital SCI unit. An episode of AD was defined as either (i) signs or symptoms of AD with accompanying SBP noted to be over

150 mmHg, or (ii) SBP noted to be over 150 mmHg on routine, scheduled vital check. The threshold of 150 mmHg was chosen for the initial protocol study which built the database, as this is the blood pressure recommended for potential pharmacologic interventions in the Consortium Guidelines.³ Previous analysis of this dataset had demonstrated a likely minimal contribution of essential hypertension inadvertently being recorded as AD episodes.⁴ Once AD was identified by nursing staff, the protocol was initiated, encompassing escalation from conservative management to pharmacologic interventions (Fig. 1). Full details of this study protocol have been described elsewhere.⁴ Blood pressures and heart rates were taken at a minimum of every 10 minutes with an automated cuff while management was ongoing until AD was successfully managed (with threshold arbitrarily placed at SBP consistently below 160 mmHg without rebound hypertension over the subsequent three hours for timing data).

We performed analyses of this AD episode dataset to answer the following clinically relevant questions regarding this condition.

Relative bradycardia vs tachycardia during AD

Given the variability in presentations of AD, we identified the heart rate during peak SBP for each episode of AD and compared this to the individual's baseline heart rate. For the purposes of this study, the baseline heart rate was assumed to be the mean heart rate at resolution of all AD episodes for a given individual. Relative bradycardia was defined as >10 beats per minute (bpm) below the baseline heart rate, with relative tachycardia defined as the reciprocal. All other changes in heart rate within 10 bpm of the baseline were considered to be within physiological normal variations.

Effectiveness of opioid medications in nociceptive pain mediated AD

Currently, recommendations for the treatment of AD centers on removing the noxious stimulus and treating with antihypertensive medications if this fails.³ However, when the noxious stimulus is not readily eliminated (such as postoperatively or during child birth), some have advocated treating with opioids.⁵ To analyze this further, episodes of AD were identified where nursing documented the suspected cause as abdominal, musculoskeletal or post-operative pain. These were then further stratified into those where opioid pain medication was received in addition to the standardized protocol of conservative management/antihypertensives and those episodes that received the protocol without opioids. Comparative statistics were

Figure 1 Flow diagram summary of autonomic dysreflexia protocol. Full protocol appears in Solinsky et al.⁴

used to analyze each group to determine if either time to resolution of the AD episode or relative decrease in SBP differed with the addition of opioids. A single-tailed, heteroscedastic student's t-test was used to identify differences between these groups with a P value of <0.05 considered statistically significant.

Effect of chronicity of SCI on response to pharmacologic intervention

Research has demonstrated that an individual's physiology continues to evolve, even in chronic SCI.^{6,7} To assess potential changes in response to medications, AD episodes that did not resolve with conservative measures were further analyzed based on the chronicity of the individuals' injury. For this analysis, episodes of AD that were treated with the standardized pharmacologic protocol as well as those treated with additional medications outside of the protocol were included. These episodes were stratified by chronicity of injury and analyzed to determine the mean time to resolution for each cohort. Mean time of conservative management relative to chronicity of injury was also calculated.

Response to topical nitroglycerin ointment with presumed bladder related stimuli

It has been demonstrated that in addition to its antihypertensive effect, nitroglycerin acts on the external urethral sphincter to decrease resting tone in both

uninjured individuals and those with SCI.^{8,9} To analyze whether this may further have a dual effect on AD treatment in individuals with SCI (where bladder issues are a primary driver for sympathetic tone),¹⁰ we analyzed those episodes that failed conservative management and were successfully managed after nitroglycerin ointment administration (applied to the upper chest). These AD episodes were further broken down to those where the suspected source was bladder overdistension, bladder spasms, or urinary tract infection versus those with suspected non-bladder related causes. Time to onset of action of the nitroglycerin ointment, mean decrease in blood pressure (from peak to conclusion SBP), and percentage requiring additional pharmacologic treatment were compared for each group. The time to onset of action was defined as time for SBP to decrease 10 mmHg from the peak value. Time to clinically managed (SBP reaching below 160 mmHg and persisting below this threshold) was also calculated for each grouping of etiologies. Data was compared for statistically significant differences via student's t-test as above.

Results

Over a 3 $\frac{1}{2}$ year period, 445 episodes of AD in 78 hospitalized patients were prospectively recorded as part of a standardized treatment protocol administered by specialty trained SCI staff (Table 1). All individuals in this study population were male and tended to have more chronic injuries (mean chronicity of SCI of 20.2 years).

Table 1 Demographics for entire study population, *Age at time of first AD episode while inpatient during the study period.

Sex	
Male	78 (100%)
ASIA impairment scale	
A	45 (58.4%)
B	18 (23.4%)
C	6 (7.8%)
D	9 (10.4%)
Neurologic Level of Injury	
C1-C4	17 (21.8%)
C5-C8	46 (59.0%)
T1-T7	15 (19.2%)
Age*	
Mean age (min, max, SD)	55.9 years (25, 81, 13.0)
Presumed causes of AD	
Unknown	287 (64.5%)
Urinary retention	47 (10.6%)
Full bowel	29 (6.5%)
Post-operative pain	25 (5.6%)
Bowel care	24 (5.4%)
Urinary Tract Infection	11 (2.5%)
Musculoskeletal pain	11 (2.5%)
Abdominal Pain	9 (2.0%)
Urinary Stone	1 (0.2%)
Bladder Spasm	1 (0.2%)

Relative bradycardia vs tachycardia during AD

Of the 445 episodes of AD, 45 episodes were excluded from this analysis due to incomplete data on heart rate. The mean resolution heart rate was 67.4 bpm (SD 15.3). Relative tachycardia occurred in 68.0% of the 400 episodes of AD that were recorded, with 31.8% of episodes not differing more than 10 bpm from baseline, and 0.3% (n=1) of episodes demonstrating relative bradycardia. The mean heart rate change across all episodes was an increase of 20.4 bpm. 365 episodes of AD were identified in 63 individuals with cervical injuries, and 35 episodes were recorded for 15 individuals with thoracic injuries. For individuals with cervical or thoracic injuries, there were similar mean heart rate changes (increases of 20.5 and 19.7 bpm, respectively) and rates of relative tachycardia (67.9% vs 68.6%). The mean heart rate change and rate of relative tachycardia for episodes of AD attributed to nociceptive pain (previously defined) was 19.8 bpm and 64.2%. Non-nociceptive pain demonstrated

increases of 20.6 bpm with a 60.9% rate of relative tachycardia ($P=0.41$ and 0.35 respectively).

Effectiveness of opioid medications in nociceptive pain mediated AD

Within our dataset, the presumed etiology of 54 episodes of AD was identified by nursing to be post-operative/nociceptive pain (appearing in Table 1 as musculoskeletal or abdominal pain). Of these, two were treated with acetaminophen in addition to the antihypertensive protocol and were excluded to avoid confounders. Opioid pain medications given included methadone, morphine, oxycodone, and oxycodone/acetaminophen. Initial and maximum blood pressures were not significantly different between groups (Table 2, P values ranged from 0.38 to 0.64). The durations of AD episodes were greater in those episodes treated with opioids in addition to the standardized antihypertensive protocol, though this was not statistically significant ($P=0.40$).

Effect of chronicity of SCI on response to pharmacologic intervention

Data on injury chronicity was available for 72 patients, encompassing 390 episodes of AD (Table 3). The mean pharmacologic time to resolution of these episodes was plotted relative to injury chronicity (Fig. 2), and a strongly matched positive linear correlation was identified ($R^2=0.83$, $P<0.001$). Data on the duration of conservative management was available for 135 AD episodes and decreased from an average of 21.5 minutes to 9.8 minutes as chronicity of injury increased (Table 3). Presenting blood pressures were similar regardless of chronicity of SCI, (186/98 for those <5 years since SCI and 184/101 for those injured >25 years).

Response to topical nitroglycerin ointment with presumed bladder related stimuli

Episodes of AD that were successfully managed after nitroglycerin ointment administration were identified, with 34 felt to be bladder related by nursing (bladder

spasms, urinary retention, or urinary tract infection) and 60 episodes felt to be non-bladder related (full bowel, post-operative pain, bowel care, musculoskeletal pain, abdominal pain). The mean time to onset of action of topical nitroglycerin for bladder related episodes was 10.8 minutes vs. 15.9 minutes for non-bladder related episodes ($P=0.18$). The mean time to reach the sustained SBP <160 mmHg was 16.5 minutes for bladder related episodes and 20.9 minutes for non-bladder related episodes ($P=0.23$). Mean peak SBP for the bladder related group was 198 mmHg versus 196 mmHg for the non-bladder related group. The mean SBP decrease for bladder related episodes was 84.3 mmHg, whereas the non-bladder related episodes decreased a mean of 68.6 mmHg ($P=0.02$). With regard to the step in the protocol required to successfully manage each episode, those with bladder sources were managed with topical nitroglycerin ointment in 34 of 41 episodes (82.9% managed rate) vs 72.3% (60 of 83 episodes) in those with non-bladder sources of AD. Unresolved episodes were treated with escalated pharmacologic treatment as per the antihypertensive protocol (Fig. 1).

Discussion

Multiple clinical and pathophysiologic insights related to autonomic dysreflexia emerge from these results. While bradycardia is typically mentioned as a primary sign accompanying hypertension in AD,³ relative tachycardia was seen in the majority of our observed AD episodes. Kewalramani¹¹ previously noted only 10% of AD episodes had true bradycardia, with 38% presenting with tachycardia. In urodynamics induced AD, Huang *et al.* noted only 22.7% of SCI patients had heart rate decrease of more than 10 bpm from baseline.¹² The high frequency of relative tachycardia we observed did not appear to be pain mediated, as both the rate of relative tachycardia and the mean heart rate change in AD episodes due to suspected nociceptive sources were not notably different from those due to other sources. The

Table 2 Response of autonomic dysreflexia due to suspected postoperative/nociceptive pain to standardized antihypertensive treatment protocol with and without opioids. "Average step at resolution" refers to the pharmacologic step in Figure 1 of our standardized antihypertensive treatment algorithm, which AD episodes resolved at.

	<i>n</i>	Initial SBP/ DBP (mmHg)	Max SBP/ DBP (mmHg)	AD Episode Time	SBP Drop (mmHg)	Average Step at Resolution
Protocol with opioids	23	183.3/102.3	195.8/108.7	89.9 min	63.7	2.1
Protocol without opioids	31	182.1/103.2	198.3/112.7	72.3 min	63.2	1.6

Table 3 Distribution chronicity of SCI and duration of conservative treatment.

Years since injury	n	Duration of conservative measures (min)
<5 years	19	21.5
5–15 years	10	19.3
15–25 years	14	9.7
>25 years	29	9.8

high prevalence of relative tachycardia may be from not having a true baseline heart rate, as mean resolution heart rate was used as a proxy. This effect could be amplified if the antihypertensive medications caused a bradycardic response at AD episode resolution in this population, leading to the appearance of tachycardia when at the peak of AD. However, in previous literature of SCI patients,⁸ tachycardia has been demonstrated after sublingual nitroglycerin, arguing against this potential mechanism. Karlsson¹³ postulated that the variable tachycardic response in AD might be due to impaired sympathetic innervation of the heart and suggested that evidence for this may be differences in heart rate during AD of those with cervical vs thoracic level injuries. Our analysis, while containing only 35 episodes of AD in individuals with thoracic SCI, did not demonstrate an appreciable difference in magnitude of heart rate change or frequency of relative tachycardia when compared to those with cervical SCI.

It is possible that the relative tachycardia we consistently observed was due to discomplete autonomic injury or the spread of overriding sympathetic tone involving sympathetic cardiac efferent fibers. Multiple past studies have been supportive of increased spinal cord interconnectivity following SCI,^{14,15} with early competitive synaptogenesis occurring within the injured spinal cord in the absence of supraspinal signals.¹⁶ A trend toward greater tachycardic response with increased chronicity of injury was not seen in our data, arguing against ongoing evolution of any potential

pathophysiology. Whatever the mechanisms, it is notable that a significant proportion of individuals with SCI may present with relative tachycardia as opposed to bradycardia during AD. Further well controlled studies are needed to explore these findings. While easily identified on the check of vital signs, we argue that heart rate should be less of a strict criterion for determining if a patient has AD (similar to sweating or flushing).

Our data demonstrates that the addition of opioids to standardized antihypertensive medications was not associated with decreased duration of AD episodes or a more profound SBP decrease. Due to the uncertainty of the timing of non-protocolled medications, episodes of AD treated with opioids may have been prolonged to start, with opioids incorporated late in an effort to further curb the response when the protocol seemed to be ineffective. Further, the variety of doses and types of opioids used in these observations introduces heterogeneity to the data, and caution should be taken in the interpretation.

Opioid receptors exist throughout the spinal cord¹⁷ and when bound suppress intraspinal excitability through release of GABA neurotransmitter. However, oral morphine has extensive first pass metabolism in the liver, with peak blood levels taking 30–90 minutes to reach. Based on this, it is reasonable to concur that even though opioids may help downregulate sympathetic cascades within the spinal cord, they may take longer to have the desired effect of blood pressure control during AD. While opioids potentially have neuroregulatory effects on AD, our study was unable to identify these effects, which may have been masked by our pairing of relatively slow acting opioids with fast acting antihypertensives. In cases of recalcitrant AD due to nociceptive pain, the timeline for opioids to exhibit this proposed neuroregulatory effect may be more relevant. Further research is needed to explore the role of opioids on autonomic dysreflexia, though no significant improvement in episode resolution time was noted in our data when these medications were added.

Chronicity of SCI demonstrated a strong positive linear correlation with increased pharmacologic time to resolution of AD episodes. This is consistent with emerging evidence for ongoing evolution within the spinal cord well after the initial injury, where both a greater degree of AD⁶ and a higher rate of detrusor sphincter dyssynergia¹⁸ have been noted as SCI becomes more chronic. Further, in chronically injured animal models, increased alpha-1 adrenergic receptor expression has been noted in arteries, potentially

Figure 2 Chronicity of SCI vs. mean time to resolution of pharmacologically treated autonomic dysreflexia episodes.

leading to an amplified vascular response to sympathetic influx.¹⁹ The delayed response to medications we observed in chronically injured patients may also be from other causes of external blood pressure elevation such as an increased degree of other sympathetic tone generated from delayed colonic transit times²⁰ or concomitant essential hypertension.

While research in uninjured individuals has demonstrated no clinically important tolerance to long term nitrates,²¹ it is unclear the cumulative resistance of these medications in individuals with altered physiology due to SCI. The strong linearity of the association between chronicity of SCI and impedance to resolution may signal an underlying pathophysiologic explanation such as the maturation of entrenched interneuronal networks to amplify these sympathetic signals. Over time, the combination of underlying essential hypertension and fortified intraspinal circuits may both lead to the significant findings we observed. The decreasing amount of time spent on conservative management with regard to increased injury chronicity may signal patients seeing medications as an eventuality for AD management and being more apt to ask for these at earlier timepoints. Given the multiple potential causes of these findings and unclear clinical significance, further well designed studies are warranted to explore this issue.

The relationship between bladder distension and hypertension has been well established,²² yet the potential preferential role of nitroglycerin in regulating bladder induced AD has only minimally been implied. Reitz *et al.*⁸ noted a decrease in external urethral sphincter tone with administration of nitroglycerin, and our results did show a greater decrease in SBP over a shorter duration with nitroglycerin ointment in those with bladder related AD. However, only this decrease in systolic blood pressure, and not time to effect or time to reach safe blood pressure was statistically significant. Given the chronicity of our patients, this lack of significant difference in time to see response from the nitroglycerin ointment may not be unexpected. Previous research has demonstrated that bladder tone and spasticity increasingly becomes more dependent on usually silent C-fibers in the bladder wall over time.^{23,24} What's more, it has been shown that blocking these spastic bladder signals in SCI patients can decrease normally unrelated neighboring spinally mediated H-reflexes.¹⁵ This suggests that a complex system of interconnectivity exists and moderates action potential thresholds within the spinal cord below the neurological level of injury following SCI. With aberrant spinal networks reinforced over time in this chronically injured population, the ability of sphincter relaxation to

dampen an existing sympathetic cascade may be degraded. Further research is needed to build additional evidence on if nitroglycerin has a more pronounced role in bladder mediated AD in those with less chronic injuries.

Limitations

The retrospective nature of this analysis limits the ability to control against potential outside variables. As our data is based in part on presumed etiology, and accurately recording opioids and timing in free text fields, it is not possible to correct for errors caused by differences in clinical experience or incomplete recording. Particularly, when comparing presumed etiologies of AD, our data is additionally limited in the over 60% of episodes where no offending stimuli was recorded/identified. Further, the International Classification to document remaining Autonomic Function after SCI (ISAFSCI) defines AD as an elevation of 20 mmHg over baseline SBP.²⁵ We were limited by our existing data and used our original, pre-ISAFSCI, definition of AD as SBP greater than 150 mmHg. This may have caused us to miss a number of low grade AD episodes, which resolved with conservative management alone. Additional limitations stem from the definition of successfully managed AD as a consistent SBP below 160 mmHg (as opposed to 150 mmHg or baseline SBP) and our lack of a true baseline heart rate. Our study population was also entirely male and considerably skewed towards chronic injuries. The latter was taken into consideration in interpretation of results, though indicates the clinical patterns and underlying mechanisms may be altered in more acutely injured individuals. Given these limitations, further prospective studies are indicated to fully elucidate the nature of the underlying altered physiology suggested by this study.

Conclusion

This analysis provides several insights into AD. First, a high rate of relative tachycardia occurred with AD in our study. The addition of opioids did not significantly decrease time to, or attenuation of, hypertension associated with AD, though our study was not ideally constructed to answer this question. Increased chronicity of SCI was strongly associated with prolonged duration of pharmacologically treated AD events. Finally, the use of nitroglycerin ointment for bladder mediated AD did appear to have a more accentuated effect, though only reached statistical significance with respect to the magnitude of decrease in SBP. Further targeted studies are warranted to better inform the observations and proposed mechanisms that emerge from these findings.

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