

## ORIGINAL ARTICLE

# Autonomic dysreflexia during bowel evacuation procedures and bladder filling in subjects with spinal cord injury

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## INTRODUCTION

Autonomic dysreflexia (AD) is a common and potentially life-threatening complication to spinal cord injury (SCI) at or above the sixth spinal cord thoracic segment (T6).<sup>1</sup> It is a constellation of signs and symptoms including headache, feeling of anxiety, bradycardia, cardiac arrhythmias, profuse sweating above the level of injury, piloerection and flushing, pale and dry skin below the level of injury, blurred vision and nasal congestion<sup>2</sup> occurring in response to usually noxious, but sometimes also nonnoxious, stimuli below the level of spinal cord lesion. The pathophysiology of AD is not completely understood but includes widespread uncontrolled sympathetic activation followed by vasoconstriction and increased blood pressure (BP).<sup>3</sup> The clinical presentation of AD varies from asymptomatic<sup>4</sup> to life-threatening emergencies with systolic blood pressure (sBP) of  $\geq 300$  mm Hg.<sup>2</sup>

Neurogenic bowel and bladder are common consequences of SCI. Both rank among the top three symptoms affecting the quality of life of patients with SCI.<sup>5</sup> Clean intermittent catheterization is arguably the preferred approach for neurogenic bladder management in people with SCI at or above T12.<sup>6</sup> Neurogenic bowel dysfunction may prove more difficult in clinical practice and most subjects with SCI need digital anorectal stimulation/evacuation or suppositories to induce defecation.<sup>5,7</sup> Transanal irrigation (TAI) with enema administered through special rectal catheters results in evacuation of the distal

colorectum<sup>8,9</sup> and has proven effective for severe neurogenic bowel dysfunction.<sup>8,10</sup> TAI is commonly used in Europe and it has recently been introduced in the United States for management of neurogenic bowel dysfunction. Usually, 500–1000 ml of lukewarm tap water is installed every to every third day and for most patients the procedure takes between 30 and 45 min.

Otherwise unrecognized stimuli from the bladder and gut are common causes of AD<sup>11</sup> and many patients have symptoms of AD during standard bowel emptying procedures.<sup>5,8</sup> In spite of this, autonomic responses to bladder filling and bowel emptying procedures have only been scarcely investigated. In addition, it is unknown whether irrigation, usually with  $\sim 500$ –1000 ml, carries a higher risk of inducing AD than standard bowel emptying procedures. Accordingly, the aim of the present study was to describe and compare autonomic responses during (1) bladder filling, (2) digital anorectal stimulation/evacuation and (3) TAI in patients with SCI.

## MATERIALS AND METHODS

### Subjects

Adult SCI patients were consecutively evaluated for inclusion from the Anorectal Physiology Unit, Aarhus University Hospital or from the Spinal Cord Injury Clinic, Viborg Hospital, Denmark. Patients were considered for inclusion if they either had (1) complete SCI (AIS A) at or above

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the sixth spinal cord thoracic level (T6) and a previous history of AD or (2) complete SCI (AIS A) between tenth thoracic (T10) and second lumbar (L2) segments. Exclusion criteria were previous major intraabdominal surgery, systemic medication altering bowel or bladder function, major psychiatric disease, inability to understand information and give informed consent and current disease impairing participation (for example, pressure ulcer, severe spasticity or urinary tract infection). Thorough instruction with emphasis on safety and treatment of AD was given to all participants and staff. The study was performed in accordance with the Helsinki II declaration and was approved by the Ethics Committee, Central Denmark Region (ID 2009-0112). The study was registered on ClinicalTrials.gov (ID NCT01059370).

Among 57 patients referred to the two centers, 34 fulfilled the inclusion criteria. Nine with high SCI and three with low SCI accepted to participate. Baseline information obtained included The International Bowel Function Basic Spinal Cord Injury Data Set,<sup>12</sup> The Autonomic Standard Assessment Form<sup>13</sup> and demographic data including age, gender and use of medication. Three patients with high SCI were treated with baclofen administered with an intrathecal pump. A 4-week diary of daily AD episodes was completed before and after trial participation.

### Experimental protocol

All examinations were performed in the fasting state and in a standard setting with at least 4 h between examinations. The order of examinations was random and determined by drawing a sealed envelope allocating 2 of the 12 subjects to each of the six possible orders of three stimuli.

For bowel emptying procedures participants were seated on a commode in the upright position. For the filling cystometry they were seated as upright as possible in a hospital bed. Throughout the three examinations blood pressures and heart rate were monitored with the Finometer PRO (Finapres Medical Systems BV, Amsterdam, The Netherlands). The Finometer PRO determines blood pressure for every contraction of the heart. The filling cystometry (FC) was performed with Menuet (Dantec, Skovlunde, Denmark). Three blood samples were taken for analysis of norepinephrine and epinephrine levels: (1) after 10 min of stable baseline BP and heart rate measurements, (2) 3 min after maximum stimulation and (3) 12 min after maximum stimulation. As a precaution, poststimulation BP and heart rate were monitored until reaching baseline levels.

Digital anorectal stimulation/evacuation and TAI were performed by the same experienced bowel specialist nurse. All participants had an empty bladder during bowel evacuations. The FC was performed by another bowel and bladder specialist nurse. Examinations were performed in a standard manner as recommended by Coggrave and Norton.<sup>14</sup> Thus, digital rectal evacuation (DE) was performed once or twice lasting no longer than 5 to 10 min. TAI was performed with the Peristeen anal irrigation system (Coloplast AS, Humlebaek, Denmark). The bowel nurse inserted the catheter into the rectum of the patient, inflated the catheter balloon with 30 to 60 ml of air, and installed 500 ml lukewarm water into the rectum. Administration of the enema lasted 5–10 min. Afterwards the catheter was removed and the enema and stools would empty into the commode. FC was performed on an empty bladder with infusion of tepid, sterile saline at a rate of 50 ml per min. The procedure was stopped when a maximum of 500 ml was installed, or when reaching the individual previously determined FC value. All three examinations were terminated after standard stimulation if severe subjective symptoms of autonomic dysreflexia occurred, or if sBP increased by 75% of resting values. Maximum stimulation was defined for each of the three stimuli as the time when (1) 500 ml had been installed in the bowel (transanal irrigation), (2) the FC volume or the maximum of 500 ml had been reached (bladder filling) and (3) just before digital stimulation was stopped (digital stimulation). Autonomic dysreflexia was defined as an increase in sBP of at least 30 mmHg above baseline.<sup>1</sup>

Epinephrine and norepinephrine were measured by radioimmunoassay using a commercial kit (2-Cat RIA, Labor Diagnostika Nord, Nordhorn, Germany). Intra- and inter-assay variations for the analyses are 4.6% and 6.1% respectively.

### Statistical analysis

Data analysis was performed with the computer program STATA/IC 10 for Windows (StataCorp, College Station, TX, USA). As data deviated from the normal distribution (determined by normal probability plots), the nonparametric Wilcoxon's signed-rank test was used for comparisons. Descriptive statistics were performed on background data.  $P < 0.05$  was considered statistically significant.

### RESULTS

Eight subjects with SCI (AIS A) at or above T6 and three with SCI (AIS A) at T10–L2 completed the study according to protocol after reaching maximum stimulation. For this paper, the two groups will be referred to as high SCI and low SCI, respectively. One participant with high SCI did not complete the study as she had severe AD early in her first examination. For safety reasons she was excluded from further study. At baseline with subjects sitting in the upright position just before the first examination, one participant with high SCI had mild hypertension (154/88 mm Hg) and one with low SCI had moderate/severe hypertension (181/99 mm Hg). All signs of AD had disappeared before the subjects left the unit. Demographics are presented in Table 1 and baseline autonomic and gastrointestinal functions in Tables 2 and 3.

All eight remaining participants with high SCI had AD during all examinations (Figure 1 and Table 4). However, sBP increased less during TAI (36 mm Hg, range 30–63) than during digital evacuation (57 mm Hg, range 41–75;  $P < 0.05$ ) or FC (61 mm Hg, range 55–100;  $P < 0.02$ ). The difference in sBP response between digital evacuation and FC was nonsignificant ( $P = 0.09$ ). Median 'time at risk', defined as sBP above 150% of baseline sBP, was 3 min (range 2–14) during digital evacuation, 4 min (range 2–9) during transanal irrigation and 4 min (range 2–7) during filling cystometry ( $P > 0.53$ ). During all three procedures, subjective symptoms of AD occurred in seven of eight subjects with high SCI. One participant with a traumatic T5 (AIS A) lesion had asymptomatic AD during all three procedures.

According to our definition of AD as an increase of at least 30 mmHg above sBP, none of the subjects with low SCI had AD or symptoms of AD during any of the procedures. There was no difference in sBP response during TAI (16 mmHg, range 12–18)

**Table 1** Demographic data

	Subjects with high SCI (n = 8, 6M and 2F)	Subjects with low SCI (n = 3, 2M and 1F)
Age in years (median, range)	52 (41–69)	51 (47–57)
Years since SCI (median, range)	17 (3–27)	9 (7–26)
Level of complete injury (AIS A)	C5 in 1 C6 in 2 T3 in 1 T4 in 1 T5 in 2 T6 in 1	T10 in 1 L2 in 2
<i>Traumatic etiology</i>		
Traffic accident	6	1
Fall	2	
<i>Nontraumatic</i>		
Disc disease		1
Tumor		1
AD occurring daily (n, %)	3 (37.5%)	None

Abbreviations: AD, autonomic dysreflexia; F, female; M, male; SCI, spinal cord injury.

**Table 2 Autonomic function**

<i>The Autonomic Standard Assessment Form</i>	<i>Subjects with high SCI (n = 8)</i>	<i>Subjects with low SCI (n = 3)</i>
<i>HR</i>		
Normally controlled	7	3
Tachycardia	1	0
<i>BP</i>		
Normally controlled	0	3
AD	8	0
<i>Sweating</i>		
Normally controlled	1	1
Hyperhidrosis above lesion	6	2
Hyperhidrosis below lesion	2	0
Hypohidrosis below lesion	2	0
<i>Temperature</i>		
Normally controlled	2	2
Hyperthermia	2	1
Hypothermia	3	0
Unknown	1	0
<i>Bronchopulmonary system</i>		
Normally controlled	6	3
Full ventilatory support	1	0
Impaired, no vent support	1	0
<i>Bladder</i>		
Awareness to empty bladder	5 (all 5 indirect)	3 (all 3 indirect)
Ability to prevent leakage	0	3 (2 reduced)
Intermittent catheterization	3	2
Suprapubic catheter	3	0
Urinary sheath	2	1
<i>Bowel</i>		
Sensation of bowel movement	4 (all 4 indirect)	3 (all 3 indirect)
Continence	2	3 (2 reduced)
Voluntary sphincter contraction	0	0
<i>Sexual function</i>		
Genital arousal	6 (6 psychogenic and 4 reflex stimulation)	3 (2 reduced psychogenic and 0 reflex stimulation)
Orgasm	2 (2 reduced)	1
Ejaculation	2 (2 reduced)	0
Sensation of menses	1 (1 indirect)	1 (1 indirect)

Abbreviations: AD, autonomic dysreflexia; BP, blood pressure; HR, heart rate; SCI, spinal cord injury.

Autonomic function among patients included in the study assessed with the Autonomic Standards Assessment Form (22) is shown.

compared with digital evacuation (15 mm Hg, range 13–22;  $P = 0.28$ ) or FC (12 mm Hg, range 11–17;  $P = 0.10$ ).

After all three procedures, blood levels of norepinephrine taken 3 min after maximum stimulation were significantly above baseline in subjects with high SCI (Table 4). There was no difference between the levels reached during the three stimuli ( $P > 0.60$ ). At 12 min after maximum stimulation, levels of norepinephrine were no longer statistically higher than at baseline (Table 4). Blood levels of

**Table 3 Bowel function**

<i>The International Bowel Function Basic Spinal Cord Injury Data Set</i>	<i>8 Participants with high SCI (n)</i>	<i>3 Participants with low SCI (n)</i>
GI or anal dysfunction before SCI	0	0
Abdominal surgical procedures	0	0
<i>Awareness of the need to defecate</i>		
Indirect	4	3
<i>Defecation method (main)</i>		
Straining/bearing down	0	1
Transanal irrigation	3	0
Mini enema ( $\leq 150$ ml)	3	0
Suppositories	0	1
Digital stimulation or evacuation	2	1
<i>Defecation method (supplementary)</i>		
Digital stimulation or evacuation	7	3
Suppositories	1	0
<i>Time required for defecation</i>		
0–5 min	1	0
11–20 min	2	2
21–30 min	2	1
31–60 min	1	0
> 60 min	2	0
<i>Frequency of defecation</i>		
Once a day	6	1
Not daily but more than twice a week	2	1
Not every week but more than once a month	0	1
<i>Frequency of fecal incontinence</i>		
Daily	1	0
Not daily but at least once a week	0	1
Not every week but more than once a month	1	0
Less than once a month	2	1
Never	4	1
<i>Need to wear pad or plug</i>		
Daily	1	0
Not every week but at least once a month	1	1
Medication affecting bowel function	0	0
<i>Oral laxative use</i>		
Osmotic laxatives	7	1
Irritant laxatives	1	0
<i>Perianal problems</i>		
Hemorrhoids	2	1
Perianal sores	1	0
Fissures	1	0

Abbreviations: GI, gastrointestinal; SCI, spinal cord injury.

Bowel function among patients included in the study assessed with the International Bowel Function Basic Spinal Cord Injury Data Set (21) is shown.

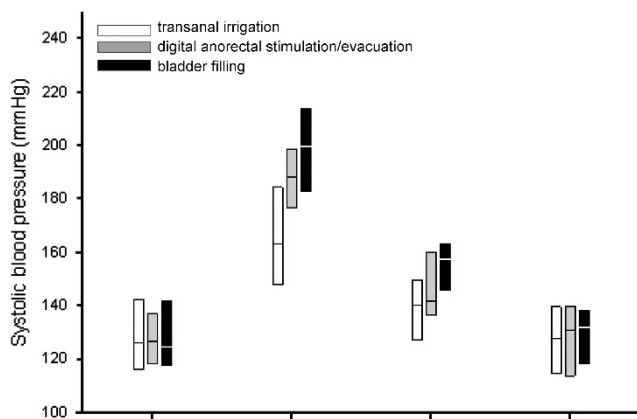
epinephrine did not increase significantly above baseline values during any of the procedures ( $P > 0.16$ ).

In patients with low SCI, blood levels of norepinephrine and epinephrine did not increase during investigations.

In comparing data from dairies in the weeks before and after investigations, no consistent change in AD symptoms was found.

## DISCUSSION

In the present study, all subjects with high SCI had AD during bladder filling, digital anorectal stimulation and transanal colorectal irrigation. Our study for the first time demonstrated a significant difference in the severity of AD in the same population with various bladder- and bowel-related procedures. Stimuli from the lower urinary tract are generally considered the most common causes of AD. During standard urodynamic examinations, it has been reported that 43% of patients with lesions at or above T6 and 15% of patients with lesions below have AD.<sup>15</sup> In a retrospective study of 571 Japanese patients with high SCI, symptomatic AD was mainly associated with use of reflex voiding and manual removal of stool.<sup>16</sup> In contrast, subjects who were continent on spontaneous voiding and defecation had the lowest prevalence of AD.



**Figure 1** Systolic blood pressure (median and range) during bladder filling (black), transanal colorectal irrigation (white) and digital anorectal stimulation/evacuation (gray) in subjects with high SCI. Results are given for baseline, maximum stimulation (Max.stim.), 3 min after maximum stimulation (+3min) and 12 min after maximum stimulation (+12min). The boxes are displayed slightly offset for better reader friendliness.

Transanal colorectal irrigation is increasingly used for the management of neurogenic bowel dysfunction and the clinical effect has been documented in a European, randomized, multicenter trial.<sup>8</sup> During transanal irrigation, 500–1000 ml are administered to the rectum and distal colon. Before the present study, it was unknown whether this could prove a strong stimulus for AD and if patients with a history of AD should be restricted from the use of irrigation. Our data indicate that irrigation causes less severe AD than bladder filling and standard digital anorectal stimulation. This was somewhat surprising, but the data are supported by a previously reported trend towards less symptoms of AD during irrigation as compared with standard bowel management.<sup>8</sup>

Episodes of AD are frequently associated with various signs and symptoms that could be life threatening.<sup>2</sup> Although numerous mechanisms for the development of AD have been proposed and examined, the pathophysiology is still not completely understood.<sup>11</sup> The clinical hallmark of AD is an abrupt increase of sBP and usually the definition is a rise of at least 20 or 30 mmHg above baseline pressure.<sup>17</sup> The sympathetic discharge during AD is triggered by noxious or nonnoxious stimuli below the level of lesion.<sup>18</sup> Recent data from animal studies suggest that TRPV1 (transient receptor potential vanilloid 1)-mediated stimuli from the colorectum are involved in conveying the stimuli that trigger episodes of AD.<sup>19</sup> Axons of the sensory neurons from the thoracolumbar and lumbosacral dorsal root ganglia expressing TRPA1 (transient receptor potential ankyrin 1) are present in the pelvic nerves that reach the distal colon.<sup>20</sup> It is believed that TRPV1 neurons are involved in the regulation of colonic motor function, but usually not in nociception.<sup>21</sup> TRPA1 is necessary for normal mechanosensory function and the signaling of noxious mechanical stimuli.<sup>21</sup> It remains to be shown whether stimulation of other colorectal mechanoreceptors causes AD.

In contrast to the colon and the rectum, the anal canal is densely innervated by afferent nerve fibers. This may explain our observation that digital anorectal stimulation was a more powerful stimulus for AD than transanal colorectal irrigation. As two-thirds of subjects with SCI use digital anorectal stimulation or evacuation, and 37% of patients have mild symptoms of AD during bowel evacuation,<sup>5</sup> a clinical

**Table 4** Autonomic response to bowel and bladder procedures

	Baseline	Maximum stimulation	At 3 min after maximum stimulation	At 12 min after maximum stimulation
<i>Transanal irrigation</i>				
sBP (mm Hg)	126 (91–146)	164 (130–188)*	140 (103–152)*	128 (104–145)
dBP (mm Hg)	73 (61–87)	91 (76–101)*	80 (68–125)*	77 (50–96)
HR (b.p.m.)	71 (56–94)	66 (53–91)	71 (56–101)	77 (50–113)
Norepinephrine (nmol l <sup>-1</sup> )	2.66 (0.49–3.52)	—	2.965 (0.47–4.17)*	3.09 (0.5–3.55)
Epinephrine (nmol l <sup>-1</sup> )	0.055 (0.03–0.22)	—	0.05 (0.03–0.42)	0.08 (0.009–0.51)
<i>Digital anorectal stimulation</i>				
sBP (mm Hg)	127 (86–154)	188 (140–206)*	142 (102–167)*	131 (83–147)
dBP (mm Hg)	76 (60–96)	110 (87–134)*	90 (66–102)*	75 (47–89)
HR (b.p.m.)	81 (60–98)	72 (32–98)	82 (52–98)	83 (53–95)
Norepinephrine (nmol l <sup>-1</sup> )	2.26 (0.049–3.06)	—	3.04 (0.4–3.86)*	2.24 (0.33–3.42)
Epinephrine (nmol l <sup>-1</sup> )	0.09 (0.02–0.14)	—	0.08 (0.03–0.24)	0.055 (0.009–0.14)
<i>Bladder filling</i>				
sBP (mm Hg)	125 (106–149)	200 (179–220)*	158 (142–172)*	132 (105–153)
dBP (mm Hg)	77 (54–90)	109 (80–127)*	87 (67–106)*	79 (64–86)
HR (b.p.m.)	74 (46–105)	60 (41–99)	66 (42–103)	73 (49–113)
Norepinephrine (nmol l <sup>-1</sup> )	2.4 (0.39–4.28)	—	2.91 (0.87–5.95)*	2.81 (0.37–5.95)
Epinephrine (nmol l <sup>-1</sup> )	0.05 (0.009–0.17)	—	0.06 (0.009–1.02)	0.07 (0.009–0.26)

Abbreviations: b.p.m., beats per min; dBP, diastolic blood pressure; HR, heart rate; sBP, systolic blood pressure.

Autonomic response to transanal colorectal irrigation, digital anorectal stimulation and bladder filling in the eight subjects with high spinal cord injury is shown. All these eight subjects with high spinal cord injury had autonomic dysreflexia during maximum stimulation, but sBP had returned to baseline 12 min after maximum stimulation.

\*Statistically significant increase compared with baseline values ( $P < 0.05$ ).

implication of our study is that TAI could be considered as an alternative in patients with severe AD during digital bowel evacuation.

Numerous previous studies documented that resting catecholamine levels, particularly norepinephrine, are low following cervical SCI. This is due to sympathetic hypoactivity.<sup>22</sup> However, during the episodes of AD there is activation of the spinal sympathetic circuits that result in prompt elevation in levels of plasma norepinephrine but not epinephrine. Similar to previous observations, AD in our subjects was also associated with significant increase in serum norepinephrine levels. Although there were significant differences in the severity of AD episodes between the various procedures tested, this was not reflected by the levels of the norepinephrine.

Episodes of AD are usually short lasting once the stimulus is removed. Our data support the clinical approach of immediately removing the stimulus for AD.<sup>23</sup> Thus, sBP and elevated blood levels of norepinephrine quickly fell as soon as stimulation was stopped and returned to baseline within 12 min. The risks associated with AD are difficult to estimate. Intracerebral hemorrhage and deaths have been reported, but AD may be silent and some cases of sudden unexplained death in subjects with SCI may be caused by AD. Usually, the severity of AD is described as the maximum change in sBP but 'time at risk' with sBP above a certain level may be equally important for risk analysis. Numerous treatments of AD have been attempted.<sup>24</sup> Of special relevance to the present study, topical administration of lidocaine may be attempted in patients with repeatedly severe AD in response to digital anorectal stimulation.

For the present study we applied bladder and bowel stimuli as close to our clinical practice as possible. Thus, digital anorectal stimulation/evacuation was performed as proposed by Coggrave and Norton,<sup>14</sup> TAI was done with a standardized volume and inflow and bladder filling was done as during cystometry. Individual patients may have daily routines different from those used in the present study and, in general, bowel emptying procedures performed at home were more time consuming than allowed for in the present study. Therefore, we may have underestimated the severity of AD during digital anorectal stimulation/evacuation. In the present study we used 500 ml for irrigation. In daily practice, most patients use between 500 and 1000 ml and we may have underestimated the autonomic response to TAI in patients using higher volumes than 500 ml. Baclofen passes the blood-brain barrier very slowly, and with the use of intrathecal baclofen the concentration in plasma does rarely exceed 5 ng ml<sup>-1</sup>. This was considered of little consequence for the present study.

Our study population was mainly selected among patients with a history AD, and the results are probably not applicable to the whole population of patients with high SCI. As our aim was to compare responses with the predefined stimuli, we do not find that the validity of conclusions is hampered by selection bias.

In conclusion, we found that TAI is a less severe stimulus for AD than bladder filling or digital anorectal stimulation. Consequently, we do not find that previous symptoms of AD should restrict patients from treatment with irrigation if it is tolerated during initial administrations. Knowledge about AD and treatment thereof is important to doctors and staff introducing patients to treatment of neurogenic bowel disorders and further studies of mechanisms and neuronal pathways responsible for the development of AD in response to stimuli of pelvic organs are needed.

#### DATA ARCHIVING

There were no data to deposit.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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