Quantitative analysis of dysautonomia in patients with autonomic dysreflexia

Authors:

Nora Cívicos Sánchez MD [1], Marian Acera [2,3], Ane Murueta-Goyena PhD [3,4] Nagore Sagastibeltza[5], Raquel Martínez PhD[5], Montserrat Cuadrado [1], ArrateOrueta MD [1], Beatriz Tijero MD, PhD [2,3,6], Tamara Fernández MD [3,6,7], Rocío del Pino PhD[3], Iñigo Gabilondo MD, PhD [3,8], María Luisa Jauregui Abrisqueta MD[1], Juan Carlos Gómez Esteban MD, PhD [2,3,6,7].

Affiliations:

[1]Spinal Cord Injury Unit, Cruces University Hospital, Baracaldo, Spain; [2]Autonomic Center (NeuroTek), San Juan de Dios Hospital. Santurtzi, Spain; [3]Neurodegenerative Diseases Group, Biocruces Bizkaia Health Research Institute, Barakaldo, Spain; [4] Department of Physiology, University of the Basque Country (UPV/EHU), Leioa, Spain; [5] Faculty of Engineering in Bilbao. University of the Basque Country (UPV/EHU); [6] Neurology Department, Cruces University Hospital, Barakaldo, Spain; [7] Department of Neuroscience, University of the Basque Country (UPV/EHU), Leioa, Spain; [8]Ikerbasque: The Basque Foundation for Science, Bilbao, Spain.

Corresponding author:

Ane Murueta-Goyena

Biocruces Bizkaia Health Research Institute, Plaza de Cruces 12, Barakaldo (Bizkaia), CP 48903, Spain

+34 946006000 ext. 7961

ane.muruetagoyena@osakidetza.eus

ORCID:

Marian Acera: 0000-0002-8333-0659

Ane Murueta-Goyena: 0000-0002-9808-6943

Beatriz Tijero: 0000-0001-9894-5712

Tamara Fernandez: 0000-0001-5666-0022

Rocío del Pino: 0000-0002-6612-4757

Iñigo Gabilondo: 0000-0001-6045-2840

Juan Carlos Gómez Esteban: 0000-0002-4697-3890

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ABSTRACT

Autonomic Dysreflexia (AD) is a life-threatening condition for individuals with cervical or high-thoracic spinal cord injury (SCI). The profile of autonomic dysfunction in AD using validated clinical autonomic tests has not been described so far, although it could be useful to identify SCI patients at greater risk of developing AD non-invasively. With this objective, 37 SCI patients (27% female) were recruited, and hemodynamic and cardiac parameters were continuously monitored to determine the presence of AD, defined as an increase of systolic blood pressure of 20 mmHg or higher after bladder filling with saline. Then, standard autonomic function testing was performed, including Deep Breathing, Valsalva Manoeuvre and Tilt Table Test. Finally, baroreflex sensitivity (BRS), and spectral analysis of heart rate and blood pressure variability were measured at rest. Catecholamines and vasopressin levels were also measured at supine and upright positions. The severity of SCI was assessed through clinical and radiological examinations. AD was observed in 73.3% of SCI patients, being 63.6% of them asymptomatic during the dysreflexive episode. AD patients displayed a drop in sympathetic outflow, as determined by decreased noradrenalin plasma levels, reduced sympathovagal balance and increased BRS. In line with decreased sympathetic activity, the incidence of neurogenic orthostatic hypotension was higher in AD patients. Our results provide novel evidence regarding the autonomic dysfunction in SCI patients with AD compared to non-AD patients, posing non-invasively measured autonomic parameters as a powerful clinical tool to predict AD in SCI patients.

Keywords: Autonomic dysreflexia, spinal cord injury, hemodynamic reflexes, autonomic nervous system, neurohormonal response, orthostatic hypotension.

INTRODUCTION

Autonomic dysreflexia (AD), also known as autonomic hyperreflexia, is a life-threatening condition that most commonly occurs in patients with cervical or high-thoracic (above T5) spinal cord injury (SCI) [1-3], developing in more than half of SCI cases [4, 5]. Clinically, it is characterized by episodes of acute hypertension resulting from sympathetic hyperactivity. One mechanism for AD is the interruption of descending input to sympathetic preganglionic neurons below the level of lesion that regulate sympathetic output to the splanchnic circulation. Over time, sprouting of nociceptive primary afferents produce maladaptive plasticity of sympathetic reflex circuit below the SCI [5-7]. The higher and more severe the injury in the spinal cord, the greater the functional impairment below the lesion level [1, 2]. AD may develop at any time after SCI and episodes are triggered in response tonoxious or non-noxious sensory stimuli below the injury (e.g., bladder distention or faecal impaction). Between 75% to 85% of times the precipitating stimulus is from urological source [8-11].

During a dysreflexive episode, the afferent impulses from lower body produce a sudden increase in sympathetic tone and vasoconstriction that rises systolic blood pressure more than 20 mmHg from baseline [9, 12]. As the vagus nerve and glossopharyngeal nerves do not transmit through the spinal cord, the cardiovagal function remains intact after SCI [5, 13], and the activated baroreflex feedback system produces a reflex bradycardia. AD resolves as soon as the causal factor is removed. However, the impaired cardiovascular autonomic control puts SCI patients are at higher risk of vascular events, such as myocardial ischaemia or fatal cerebral haemorrhage [14, 15], and AD is considered a medical emergency.

Symptoms of AD include flushing and sweating above the level of injury and anxiety, blurred vision or headache are common complaints, although some patients might be asymptomatic [6, 7, 10].Nevertheless, the presence and severity of AD is highly variable among SCI patients and does not seem to be determined by the level of injury. Few studies have assessed the frequency and severity of AD during bladder filling and emptying (e.g. via reflex micturition, or intermittent or indwelling urinary catheterisation) [10], but identifying the factors that are associated with the onset of AD to know in advance which patients with SCI will experience AD, is essential to prevent mortality and morbidity after SCI. Non-invasive and well-validated autonomic clinical

tests are nowadays available in the clinical setting. These include the evaluation of cardiovagal and sympathetic function by monitoring heart rate (HR) and blood pressure (BP) responses to different manoeuvres, such as deep breathing, Valsalva Manoeuvre or head-up tilt test. By identifying patients at greater risk of suffering AD, not only the control of AD would improve, but the rate of serious complications associated with this condition would be reduced.

Therefore, the primary objective of this study was to measure hemodynamic reflexes using validated and comprehensive clinical autonomic tests to characterize the autonomic failure in SCI patients with AD.

MATERIALS AND METHODS

This prospective cohort study was conducted at Cruces University Hospital between August 2011 and October 2018. Inclusion criteria were having cervical or thoracic SCI and age of at least 18 years. Exclusion criteria were pressure ulcers or other problems affecting the skin. Any drugs potentially influencing hemodynamic measurements were stopped in the 24 hours before the testing and patients were required empty their bowels and bladder prior to the evaluation. At study inclusion, none of the patients had a diagnosis of diabetes mellitus or a diagnosis of polyneuropathy previous to SCI.The study was approved by the local ethics committee (Basque Ethics Committee, Reference PI2013132) and patients gave written informed consent before inclusion in the study, in accordance with the tenets of the Declaration of Helsinki.

Neurological assessment

The severity of the SCI was assessed through clinical and radiological examinations, assessing motor and sensory deficits and their functional implications, based on the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) of the American Spinal Cord Injury Association (ASIA) [12]. Specifically, the ASIA Impairment Scale classifies patients into one of five categories: complete spinal injury (A), complete motor injury and incomplete sensory injury (B), incomplete motor and sensory injury (C or D depending on the extent of the deficit) or normal (E).

Autonomic nervous system involvement was assessed using the Autonomic Standards Assessment Form (ASAF) which covers general autonomic function, lower urinary tract

and bowel function, and urodynamics. Further, we gathered data on cardiovascular risk factors, such as hypertension, hyperlipidaemia, diabetes mellitus, orthostatic hypotension and overweight, as well as AD itself, using the International SCI Cardiovascular Function Basic Data Set [16]. We assessed anal sphincter tone, and all patients had recently undergone urodynamic testing.

Assessment of dysautonomia

First, patients were placed on a tilt table to rest in a supine position for 40 minutes. In this position, a blood sample was drawn (30 ml). After three minutes of head-up tilt at 60º, another blood sample was collected. Adrenaline and noradrenaline levels were quantified by high-performance liquid chromatography and vasopressin levels by radioimmunoassay. Subsequently, an indwelling urinary catheter was placed following the hospital's protocol, and non-invasive hemodynamic monitoring with Task Force Monitor (CNSystems, Graz, Austria) started. This system allows continuous monitoring of hemodynamic and cardiac parameters (impedance cardiography) at rest and after various stimuli for standard autonomic function testing. While the patient remained in the supine position, between 100 and 400 ml of 0.9% saline at 37ºC were gradually infused through the urinary catheter. Hemodynamic signals were continuously monitored, including heart rate (bpm), blood pressure (mmHg) and peripheral resistance (total peripheral resistance in dyne*s/cm^5), documenting any symptoms during the manoeuvre. The criterion for the diagnosis of AD was an increase in systolic blood pressure of at least 20 mmHg from baseline. In case of signs or symptoms of AD, the procedure was immediately halted. To finish, the bladder was gradually emptied, and the indwelling urinary catheter removed.

Then, the expiration/inspiration ratio (E:I ratio) during deep breathing was calculated, but finally these data were excluded from analysis as a considerable number of patients were unable to perform this test due to hypoventilation. In Valsalva manoeuvre, heart rate and blood pressure were continuously measured for 15 seconds, while patients exhaled against a resistance of 40 mmHg. Valsalva Ratio and blood pressure difference at phase II late and phase IV of the manoeuvre from baseline were calculated. The manoeuvre was correctly completed by 22 out of 37 patients. Finally, after at least 10-minute rest period, we assessed baroreceptor sensitivity (BRS) and performed spectral analysis of heart rate variability (obtaining the high-frequency component, HF-RR) and systolic BP variability (obtaining the low-frequency component, LF-SBP), and

calculated the low-to-high frequency power ratio (LF/HF), considered indicative of sympathovagal balance.

Tilt Table Test

Patients were monitored at rest for 10 minutes, with an empty bladder and no stimulation below the level of the SCI. The table was tilted to 60 degrees and heart rate and blood pressure were continuously monitored for 10 minutes. The procedure was stopped if the patient reported symptoms such as dizziness or fainted (syncope) or if a rapid decrease in blood pressure was observed. Neurogenic orthostatic hypotension (NOH) was diagnosed based on the international criteria of a 20 mmHg decrease in SBP and/or a 10 mmHg decrease in DBP after 3 minutes of tilting [17]. Delayed NOH was considered if NOH occurred beyond 3 minutes of tilting [17].

Statistical analysis

Means and standard deviations were calculated for quantitative variables and proportions for qualitative variables. Categorical variables were compared with Chi-square test. Continuous variables were checked for normality assumption with Shapiro-Wilks test, and tested with Mann-Whitney U test, as normality assumption was violated. Spearman rho was calculated for correlation analyses. P-values < 0.05 were considered statistically significant. All the statistical analyses were performed using the SPSS v.23 (IBM Corp, Armonk, NY, USA) and graphs were created with R version 3.6.1 and GraphPad Prism version 6 (La Jolla, CA).

RESULTS

Characteristics of spinal cord injury

A total of 37 patients with a diagnosis of SCI completed study assessment. 73% (27 patients) were men and 27% (10) women. Mean age was 42.4 ± 14.1 years (range, 17 - 77) at recruitment, with a mean duration of injury of 9.1 ± 10.7 years. At the time of SCI patients were 33.3 ± 15.6 years old (range, 17 - 68), although males tended to be younger than females at the time of injury (males 39.6 ± 13.4 vs. females 49.7 ± 13.8 years old,p=0.06). The stage of injury was acute (less than 1-year since injury) in 14 (37.8%) of patients and chronic (more than 1-year since injury) in 23 (62.2%) patients, with a similar proportion among males and females.Regarding the cause, the SCI resulted from trauma in 33 patients (89%) and had a medical cause in 4 patients (11%).

In most cases, the SCI was at the cervical level (tetraplegia) (32 patients, 86.5%), while the remaining had thoracic SCI (5 patients, 13.5%). Nine patients (24%) had at least one cardiovascular risk factor according to the International SCI Cardiovascular Function Basic Data Set. In accordance with the ISNCSCI, the most common neurological level of injury was C6 (13 patients, 35%), and the score on the ASIA Impairment Scale was A in 20 patients, B in 4, C in 5, D in 7 and E in 1.

Autonomic Standard Assessment Form

The results from autonomic function using ASAF are represented in Table 1. Briefly, 25 patients (67%) had normal autonomic control of the heart while 11 (30%) showed bradycardia. Autonomic control of blood pressure was normal in 25 patients (68%) and abnormal in 11 (29%). Autonomic and somatic control of the bronchopulmonary system was normal in 6 (16%) patients and abnormal the others (31 patients, 74%), two patients needing partial or full ventilatory support. In relation to lower urinary tract and bowel function, all patients showed an increase in the activity of the detrusor muscle, while 78% of the patients had detrusor sphincter dyssynergia.

Prevalence of Autonomic Dysreflexia

Indwelling urinary catheter was successfully placed in 30 out of 37 patients. In 7 patients, urethral stenosis (implying a risk of injury during catheter placement) or catheter intolerance (attributable to hypertrophy or thickening of the detrusor muscle) hampered safely using the catheter.

The overall incidence of AD was 73.3% (22/30). In 1 patient, the placement of the urinary catheter itself triggered AD and 8 patients did not meet AD criteria. Demographic and clinical parameters of patients with and without AD are represented in Table 2. From the 22 patients with AD, 14 patients were asymptomatic (63.6%), whereas those reporting symptoms complained about increased sweating (4/22), headache (2/22) and shivering (2/22). AD was observed in most patients with cervical SCI (21/26, 81%) but only 1 with SCI at T3 (1/4, 25%).

Among the patients that presented AD, the mean increase in SBP was 38.6 ± 14.3 mmHg, while in patients without AD, the increase was 10.3 ± 7.2 mmHg. Basal systolic and diastolic blood pressures and heart rate were comparable among the two groups

(Table 2). There was a correlation between the magnitude of maximum systolic BP and time since SCI (in months) (ρ=0.52; p= 0.004). Six out of 12 patients (50%) with acute SCI (<1 year) had AD, while a higher proportion of patients with chronic SCI (16/18, 88.9%) presented AD during bladder filling. Furthermore, AD was typically precipitated in patients with ASIA impairment scores A or B (19/22, 86%), but only in 3 out of 8 (37.5%) patients with ASIA scores of C, D or E (p=0.02).

The proportion of SCI patients presenting AD was higher in females (88.9%) than in males (66.7%), but this difference was not significant (p=0.30). Male SCI patients with AD were younger (38.6 ± 14.0 years old) than females (52.8 ± 13.7 years old, p=0.05) at study inclusion, and at SCI diagnosis (males, 26.1 ± 9.2 vs. females 46.1 ± 16.4 years old, p=0.06). However, the stage of the injury (p=0.40) and proportion of ASIA score were similar between these groups (p=0.69).

Patterns of Blood Pressure Increase

During bladder filling, two different patterns of blood pressure increase were observed (Figure 1). In 21 patients, a gradual increase in blood pressure was detected (Pattern 1). In 9 patients, a decrease in blood pressure with a subsequent rise at the end of bladder filling process was detected, forming a V-shaped waveform (Pattern 2). Patients with Pattern 2 were younger (35.2 ± 9.0 years old) than those with Pattern 1 (46.4 ± 14.6 years old, p=0.046), but we failed to find differences in the rate of AD between these groups. Also, the proportion of males / females, the level of the injury, SCI duration, ASIA impairment scale score, symptoms, dysautonomic parameters or catecholamine levels were comparable between patients presenting Pattern 1 or 2 of blood pressure increase, except for vasopressin levels in supine position which were increased in patients with Pattern 1 (Pattern 1, 5.6 ± 4.8 pg/ml; Pattern 2, 2.6 ± 1.9 pg/ml, p=0.049).

Autonomic Parameters at Rest

Baroreceptor sensitivity was higher in patients who developed AD compared to those who did not, but this difference was not statistically significant (Table 2 and Figure 2). The spectral analysis did not reveal differences in heart rate variability (HF-RR) or blood pressure (LF-DBP), but differences emerged in the LF/HF, observing a lower ratio in patients with than without AD (Table 2 and Figure 2). Among the 22 patients (out of 37) who were able to perform the Valsalva manoeuvre correctly, no differences

were observed between patients with and without AD in Valsalva Ratio or in the blood pressure difference from baseline in Valsalva phases II, II late or IV. Among patients with AD, no sex differences were found in any of these variables.

Neurohormonal activity

Neurohormonal analysis revealed significant differences in noradrenalin levels, which were lower in patients with AD than in patients without AD in supine position ($p=0.008$) and during head-up tilting ($p=0.005$), and the increase in noradrenalin levels from supine to upright position was significantly lower in patients with than without AD ($p<0.001$). We did not observe significant differences in dopamine, adrenalin, or vasopressin concentrations at any position between these groups(Table 2 and Figure 2).

Tilt Table Test

In head-up tilt at 60º, 5 patients developed NOH at 3 minutes and 8 patients met the criteria for the so-called delayed NOH. No sex-differences were observed in the prevalence of NOH. Among the 13 SCI patients with NOH, 12 developed AD more than 1 year after SCI and only one patient within the first year, while 12 patients had tetraplegia and 1 presented T3 paraplegia. Therefore, 55% of SCI patients with AD presented NOH concomitantly, but none of SCI patients without AD had NOH ($p=0.01$). We did not find differences in heart rate variability (HF) or blood pressure (LF) between patients with and without NOH, but the LF/HF ratio was significantly lower in patients with NOH (0.82 ± 0.63 vs. 1.4 ± 1.0, $p=0.036$), while the BRS was higher (NOH, 19.6 ± 11.9 vs. non-NOH, 12.6 ± 9.1, $p=0.022$). Noradrenalin, vasopressin, and dopamine levels in supine or upright positions were comparable between patients with and without NOH. Nonetheless, patients with AD + NOH had lower levels of noradrenalin compared to patients without NOH in supine (107.2 ± 170.0 vs. 145.7 ± 116.7 pg/ml, $p=0.143$) and upright (173.6 ± 334.8 vs. 318.1 ± 310.3 pg/ml, $p=0.034$) positions.

DISCUSSION

In this prospective study, we recruited 37 patients with SCI, most of them with cervical SCI, and found a high prevalence of AD evoked by the retrograde infusion of saline into the urinary bladder, simulating natural bladder filling. As far as we know, this is the first study reporting that SCI patients with AD presented lower LF/HF ratio at rest

during autonomic testing and decreased noradrenalin levels compared to SCI patients without AD. Moreover, a non-significant increase in BRS was observed and half of patients with AD presented delayed neurogenic orthostatic hypotension.

Urological interventions and urodynamic studies are procedures that pose a risk of triggering sudden increases in BP, especially in young SCI patients or patients with detrusor hyperactivity [4, 18]. In our series, the majority of patients (63.6%) did not have symptoms during the AD episode, and those who were symptomatic mainly experienced increased sweating above the level of the injury [19]. Given the severe complications that may result from poor control of AD [5, 20], identifying patients at risk of developing AD is of paramount importance. It has been well documented that AD episodes are more prevalent in SCI patients who have complete spinal cord transection, in patients with injury at the level of T6 or above, and that AD worsens over time with events becoming more frequent and extreme, which is in line with our results [21, 22]. Berget et al. [23] reported cardiovagal impairment in SCI patients with a high heterogeneity in the domains of affected autonomic functions. However, these results could have been confounded by expiratory muscle weakness of SCI patients [24], as the parasympathetic innervation to the heart remains intact and cardiovagal function is not expected to be compromised. Hitherto, to our knowledge, no prior study has determined the presence and quantified the degree of autonomic function failure in SCI patients with AD.

In the current study, using non-invasive autonomic function tests, we assessed the autonomic nervous system in routine clinical practice of patients with SCI with the aim of evaluating the cardiovagal and sympathetic autonomic function to prevent potentially harmful complications, such as AD. We showed that patients with AD presented a significant decrease in LF/HF ratio at rest and low levels of plasma noradrenaline with prominent small increase in noradrenaline on head-up tilt. According to the results of Gao et al., [25] SCI subject presented lower noradrenalin spillover at rest compared to able-bodied subjects, who corroborated previous results of Krum et al. [26]. Nevertheless, they did not compare SCI patients with and without AD. Animal experiments following SCI have revealed enhanced responses to noradrenalin released from perivascular nerves [27], selective increase in the sensitivity to phenylephrine [28], and increased expression of α1-adrenergic receptors in the arterial smooth muscle layer

[29], which could be compensatory mechanisms for decreased noradrenalin levels, in line with present results.There is less agreement about the differences observed in BRS. Grimm et al., [30] found decreased BRS in SCI patients compared to controls, whereas Gao et al., [25] observed similar BRS in SCI and control subjects. Our results provide new evidence supporting that BRS is increased at rest in SCI patients with AD compared to those without AD. Therefore, AD patients display a more sensitive baroreflex system that responds more greatly and rapidly to the same change in blood pressure compared to SCI patients without AD. This could partially explain the decreased LF/HF ratio in AD patients at rest, as the increased sensitivity of baroreceptors would mediate more pronounced vagal outflow, decreasing efferent sympathetic traffic and consequently reducing sympathovagal balance.

Regarding orthostatic hypotension, during the head-up tilt table test (at 60°), 13 patients developed NOH, 5 of them in the first 3 minutes after tilting. Most patients with NOH had chronic SCI (92%), and all presented AD concomitantly, but only 60% of AD patients had NOH. BRS was higher and LF/HF lower in patients with NOH, but we did not find differences in heart rate variability (HF), blood pressure (LF) between patients with and without NOH, although a recent study found differences in heart rate variability (HF) between such groups [31]. We observed that noradrenalin levels tended to be lower in AD patients with NOH compared to patients without NOH. Overall, these findings suggest a sympathetic failure, which was larger in SCI patients with NOH plus AD. One of the factors that may trigger orthostatic hypotension is volume depletion secondary to hypertensive crisis that promotes nocturia, as observed in ambulatory blood pressure monitoring studies [32]. SCI patients often experience NOH, and according to our results, the presence of NOH was significantly related to AD, but the absence of NOH did not exclude the possibility of experiencing AD, posing the lack of NOH as a poor predictive variable for AD.

One interesting and novel finding of our study was that we observed two types of blood pressure increase patterns during the bladder filling process; the first one was the classical pattern with a gradual rise in blood pressure and a fall in heart rate due to stimulation of the baroreceptor reflex and a second pattern, characterized by an initial fall in blood pressure with a subsequent rise. The latter was observed in younger patients. It might be that aberrant plastic changes of spinal cord are age dependent [33].

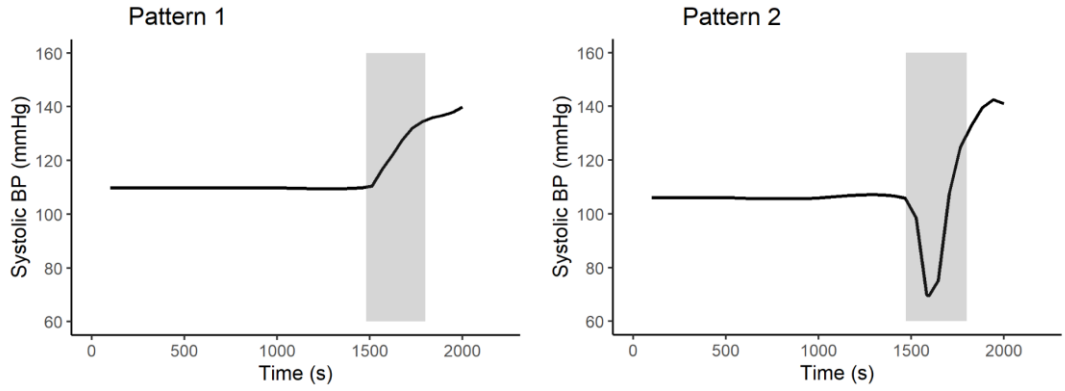
In fact, one of the few mechanisms proposed to mediate AD after SCI is the signalling of soluble Tumor Necrosis Factor alpha (TNFα) [34], whose receptors have been demonstrated to be increased in elderly people [35]. Therefore, the age dependent differences in the mechanisms for axonal repair and functional adaptation in spinal cord local circuitry could evoke divergent blood pressure responses during bladder filling. Also, high vasopressin plasma concentration, as observed in patients with Pattern 1, could enhance vasoconstriction in selected vascular beds, increasing smooth muscle contraction and systemic vascular resistance [36], preventing the blood pressure drop at the beginning of bladder filling.

This study has some limitations. First, the sample size was small and unbalanced for AD vs non-AD. Consequently, some variable means tended to be different but no significant. Second, some autonomic test could not be performed due to compromised expiratory muscle function in SCI patients. As such, heart rate variability with deep breathing as a clinical test of cardiovagal function was not analysed. It is tempting to speculate that based on present results the cardiac vagal activity was comparable in SCI patients with and without AD. Lastly, the inherent lability of autonomic testing together with the small sample size prevented us from providing cut-off values of autonomic parameters for discriminating patients with and without AD. Also, at study inclusion, the presence of polyneuropathy was not tested, and this remains a limitation of the current study. Future studies should conduct electromyogram-electroneurogram (EMG-ENG) to refine the exclusion criteria.

In conclusion, in the present study we formed a global picture of the autonomic failure in SCI patients with AD using autonomic non-invasive parameters measured after an extended rest period using beat-to-beat hemodynamic monitoring. According to our results, patients with AD displayed reduced sympathetic outflow at rest, as measured by lower plasma levels of noradrenalin, decreased LF/HF ratio, and increased BRS but with comparable blood pressures and heart rate at rest. Future studies with larger sample sizes are required to elucidate the precise quantitative limits for discriminating AD from non-AD SCI patients. Despite this limitation, the current characterization of the autonomic lesions in AD patients highlights the clinical significance of autonomic testing in SCI patients.

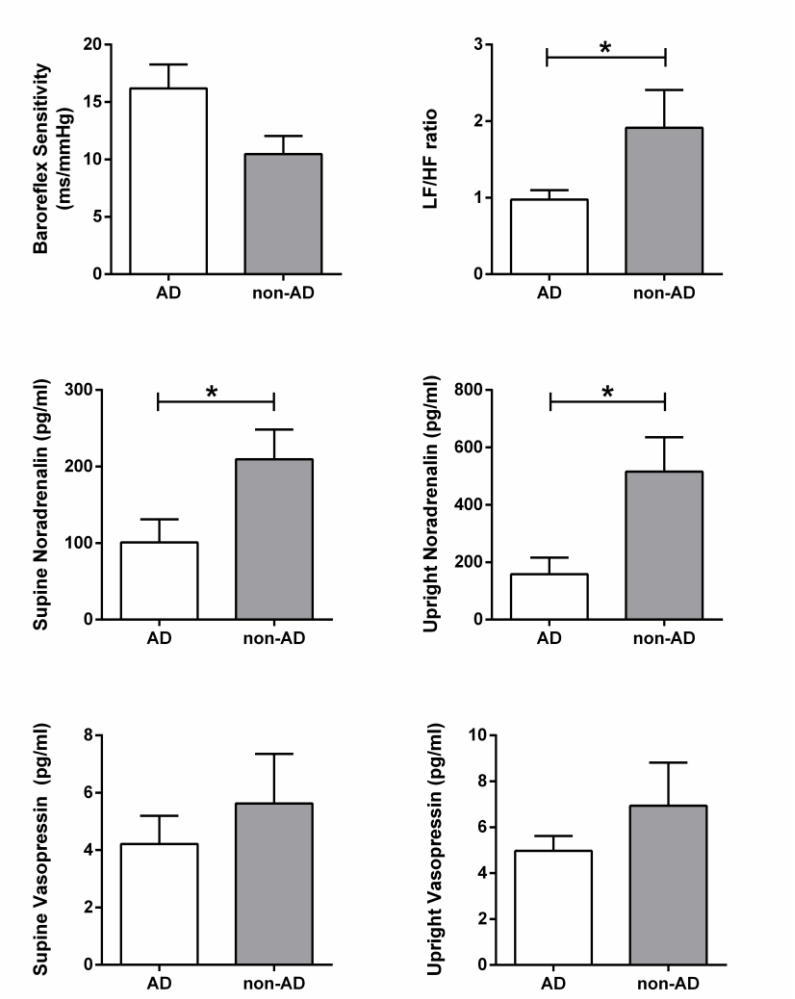
FIGURES AND FIGURE LEGENDS

Figure 1. Pattern of blood pressure rise during bladder filling with saline at 37ºC (grey shadow).



In pattern 1, a gradual increase in blood pressure was detected during filling. In pattern 2, a decrease in blood pressure with a subsequent rise at the end of bladder filling process was detected, forming a V-shaped waveform. *Abbreviations:* BP, blood pressure.

Figure 2. Measurement of resting baroreceptor reflex sensitivity, sympathovagal balance, and noradrenalin and vasopressin kinetics in spinal cord injured patients with and without autonomic dysreflexia.



Data are represented as mean ± SEM and ***** denotes a statistically significant difference of $p < 0.05$. *Abbreviations:* AD, autonomic dysreflexia; LF/HF, low frequency / high frequency ratio.

Table 1. Prevalence of symptoms measured with Autonomic Standards Assessment Form (ASAF), validated in the Spanish language.

General autonomic function	Cardiovagal function	Normal	25 (68%)
		Abnormal (bradycardia)	11 (30%) 1 unknown
	Autonomic control of Blood pressure	Normal	25 (68%)
		Unknown	1 (3 %)
		NOH	9 (24 %)
		Dysreflexia	9 (24 %)
	Autonomic control of the sweating	Normal	14 (37 %)
		Hyperhidrosis	23 (62 %)
	Temperature regulation	Normal	37 (100 %)
		abnormal	0 (0 %)
	Respiratory system	Normal	6 (16%)
		Ventilatory support	1 (3%)
		Partial ventilatory support	1 (3%)
		Hypoventilation without the need for support	29 (78%)
Lower urinary tract	Awareness of the need to empty the bladder	Normal	10 (27 %)
		Reduced function	6 (16 %)
		Complete loss of function	21 (57 %)
	Sphincters control	Normal	20 (54 %)
		Reduced function	3 (8 %)
		Complete loss of function	14 (39%)
	Bladder emptying method	Normal	11 (30 %)
		Intermittent catheterization	8 (22 %)
		Reflex	17 (46 %)
		Bladder catheterization	1 (3 %)
Bowel Function	Sphincter control and Continence	Normal	10 (27 %)
		Reduced function	7 (19 %)
		Complete loss of function	20 (54 %)
Sexual Function	Psychic excitement	Normal	1 (3%)
		Reduced function	8 (22%)
		Complete loss of function	27 (73 %)
	Reflex excitement	Normal	1 (3 %)
		Reduced function	36 (97 %)
		Complete loss of function	0 (100%)
	Orgasm	Normal	8 (22 %)
		Reduced function	4 (11 %)
		Complete loss of function	23 (62 %)
		Does not answer	2 (5.4 %)
	Ejaculation (male only)	Normal	0 (0 %)
		Reduced function	27 (100 %)
		Complete loss of	0 (0 %)

		function	
	Sensation of menses (female only)	Normal	0 (0%)
		Reduced function	4 (40 %)
		Complete loss of function	6 (60 %)
Urodynamic evaluation	Sensation during the bladder filling	Normal	8 (22 %)
		Increased	0 (0 %)
		Reduced	8 (22 %)
		Absent	21 (56 %)
	Detrusor activity	Overactive	37 (100 %)
	Sphincter	Normal urethral closure	8 (22 %)
		Dyssynergia	29 (78%)

Table 2. Demographics, clinical data, and autonomic measurements of SCI patients with and without autonomic dysreflexia.

	AD (n= 22)	non-AD (n= 8)	p-value
Age (years)	44.4 (14.4)	38.9 (12.5)	ns
Sex (male/female)	14/8	7/1	ns
Disease-related variables			
Age at SCI (years)	33.27 (15.31)	35.50 (15.92)	ns
Time since SCI (months)	124.7 (145.8)	75.1 (131.9)	ns
Symptoms (asymptomatic/symptomatic)	14 / 8	8/ 0	ns
Injury level (cervical / thoracic)	21 / 1	5 / 3	0.04
Functional injury (tetraplegia / paraplegia)	21 / 1	5 / 3	0.04
ASIA (no. of patients)	19 (A, B) 3 (C, D, E)	3 (A, B) 5 (C, D, E)	0.02
Autonomic Parameters at Rest			
Basal SBP (mmHg)	109.2 (19.4)	106.9 (5.6)	ns
Basal DBP (mmHg)	71.4 (5.3)	70.1 (16.1)	ns
HR (beats/min)	65.1 (8.1)	58.5 (8.9)	ns
BRS (ms/mmHg)	16.2 (9.8)	10.5 (4.5)	ns
LF SBP (mmHg)	1.88 (3.30)	2.31 (2.13)	ns
HF RRI (s)	1036.4 (2599.5)	210.9 (238.7)	ns
LF/HF ratio	0.97 (0.57)	1.91 (1.40)	0.02
Plasma catecholamine and hormone concentration (pg/ml)			
Noradrenalin supine	100.9 (135.6)	209.6 (109.6)	0.008
Noradrenalin upright	158.0 (248.2)	515.8 (338.8)	0.005
Adrenaline supine	25.8 (53.9)	13.4 (3.4)	ns
Adrenaline upright	16.6 (5.4)	18.3 (8.3)	ns
Dopamine supine	10.8 (2.9)	10.3 (1.0)	ns
Dopamine upright	12.9 (5.6)	15.7 (11.2)	ns
Vasopressin supine	4.2 (4.4)	5.6 (4.6)	ns
Vasopressin upright	5.0 (2.8)	6.9 (5.3)	ns
Valsalva Maneuver			
Valsalva Ratio	1.11 (0.21)	1.25 (0.29)	ns
SPB decrease at late phase II	1.6 (13.7)	10.9 (13.7)	ns
SPB increase at phase IV	1.14 (16.5)	8.4 (16.5)	ns
Tilt Test			
NOH (yes / no)	12 / 22	0 / 8	0.02

AD, autonomic dysreflexia; ASIA, American Spinal Injury Association Impairment Scale; DBP, diastolic blood pressure; HF, high frequency; LF, Low frequency; NA, noradrenalin; NOH, neurogenic orthostatic hypotension; ns, non-significant; RRI, RR interval; SBP, systolic blood pressure; SCI, spinal cord injury.

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