Sympathetic Nonadrenergic Transmission Contributes to Autonomic Dysreflexia in Spinal Cord–Injured Individuals

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Abstract—Autonomic dysreflexia is a hypertensive episode in spinal cord–injured individuals induced by exaggerated sympathetic activity and thought to be α-adrenergic mediated. α-Adrenoceptor antagonists have been a rational first choice; nevertheless, calcium channel blockers are primarily used in autonomic dysreflexia management. However, α-adrenoceptor blockade may leave a residual vasoconstrictor response to sympathetic nonadrenergic transmission unaffected. The aim was to assess the α-adrenergic contribution and, in addition, the role of supraspinal control to leg vasoconstriction during exaggerated sympathetic activity provoked by autonomic dysreflexia in spinal cord–injured individuals and by a cold pressure test in control individuals. Upper leg blood flow was measured using venous occlusion plethysmography during supine rest and during exaggerated sympathetic activity in 6 spinal cord–injured individuals and 7 able-bodied control individuals, without and with phentolamine (α-adrenoceptor antagonist) and nicardipine (calcium channel blocker) infusion into the right femoral artery. Leg vascular resistance was calculated. In spinal cord–injured individuals, phentolamine significantly reduced the leg vascular resistance increase during autonomic dysreflexia (8 ± 5 versus 24 ± 13 arbitrary units; $P=0.04$) in contrast to nicardipine (15 ± 10 versus 24 ± 13 arbitrary units; $P=0.12$). In controls, phentolamine completely abolished the leg vascular resistance increase during a cold pressure test (1 ± 2 versus 18 ± 14 arbitrary units; $P=0.02$). The norepinephrine increase during phentolamine infusion was larger ($P=0.04$) in control than in spinal cord–injured individuals. These results indicate that the leg vascular resistance increase during autonomic dysreflexia in spinal cord–injured individuals is not entirely α-adrenergic mediated and is partly explained by nonadrenergic transmission, which may, in healthy subjects, be suppressed by supraspinal control. (*Hypertension*. 2010;55:636-643.)

Key Words: autonomic dysreflexia ■ spinal cord injury ■ sympathetic nervous system
■ neurotransmitters ■ leg vascular resistance

Autonomic dysreflexia (AD) is a potentially life-threatening episodic hypertension that develops in 80% to 90% of spinal cord–injured (SCI) individuals with a spinal cord lesion at or above the sixth thoracic spinal segment (T6).[1] AD occurs in these SCI individuals because a large part of the sympathetic nervous system is without central inhibitory pathways.[2,3] An arterial pressure increase is induced by exaggerated sympathetic activity caused by visceral, noxious, or nociceptive stimuli entering the spinal cord below the level of the lesion and can be initiated by catheterization, bladder distension, and bowel evacuation.[1–4] AD is accompanied by sweating, flushing, and a pounding headache[1,4] and can lead to severe morbidity and even mortality.[5–8]

Clinically, AD has been well documented, but the mechanisms that mediate AD remain unclear.[9] Because AD is induced by exaggerated sympathetic activity, it is thought to be

α-adrenergic mediated.[2–4] Therapy with an α-adrenoceptor blocker has, therefore, been a rational first choice in AD management.[4] However, α-adrenoceptor blockers may leave a residual vasoconstrictor response to sympathetic cotransmitters, such as adenosine triphosphate (ATP) and neuropeptide Y, unaffected.[10] These neurotransmitters may still cause a vasoconstrictor response during α-adrenoceptor blockade, although their exact role during exaggerated sympathetic activity is unclear. Because SCI individuals lack supraspinal sympathetic control, their responses could differ from able-bodied individuals in the contribution of nonadrenergic transmission during exaggerated sympathetic reflexes. Nowadays, a calcium channel blocker (nifedipine) is most commonly used as a primary agent in the management of AD.[4] A calcium channel blocker may be useful to prevent or control AD, indicated by a lower blood pressure response.[11] How-

Table 1. Subject Characteristics, Including the Specific Characteristics of the SCI and Control Individuals

Subject	SCI Level	DOI, y	Age, y	Height, cm	Weight, kg	SBP, mm Hg	DBP, mm Hg
SCI1	C5	17	46	181	105	130	78
SCI2	T5	28	46	198	65	108	78
SCI3	C7	45	69	179	81	108	60
SCI4	T5	10	39	178	70	106	62
SCI5	C7	34	52	182	92	108	62
SCI6	C7	12	36	183	58	110	50
SCI	n=6		44±2	181±4	78±6	112±3	65±4
C1			22	180	67	118	76
C2			34	194	110	124	90
C3			46	174	65	118	82
C4			26	188	73	128	64
C5			42	188	88	118	78
C6			29	180	76	136	70
C7			54	187	85	138	70
Control	n=7		36±4	184±2	81±5	126±3*	76±3

Values represent mean±SD. DOI indicates duration of injury; C in column 1 indicates control subjects; SBP, systolic blood pressure; DBP, diastolic blood pressure; C, cervical spinal segment; T, thoracic spinal segment.

*Data are significantly different from SCI.

ever, the effect of calcium channel blockers on the vasoconstrictor response during AD is unknown.

The first aim was to assess the α-adrenergic contribution to leg vasoconstriction during AD in SCI individuals by α-adrenoceptor blockade. A second aim was to assess whether an α-adrenoceptor antagonist would be more effective than a calcium channel blocker in reducing the leg vasoconstriction during AD. We hypothesized that an α-adrenoceptor antagonist would abolish the leg vasoconstriction during AD and would, therefore, be more effective than a calcium channel blocker. To test this hypothesis, the effect of the α-adrenoceptor antagonist phentolamine on leg vasoconstriction during AD in SCI individuals was compared with the calcium channel blocker nicardipine (intravenous equivalent of nifedipine). The third aim was to assess the role of the presence or absence of supraspinal control on sympathetic nonadrenergic transmission during exaggerated sympathetic activity by comparing the vascular responses of SCI with those of control individuals. We hypothesized that the contribution of α-adrenergic receptor stimulation would be more pronounced in SCI individuals. To test this hypothesis, the effect of phentolamine on leg vasoconstriction during exaggerated sympathetic activity in SCI, by means of AD, was compared with control individuals by means of a cold pressor test (CPT).

Methods

Subjects

Six male SCI individuals and 7 healthy male able-bodied control individuals participated in this study (Table 1). All of the subjects were normotensive (<140/90 mm Hg; auscultatory blood pressure measurement), free of overt cardiovascular diseases, and did not report orthostatic hypotension. Two SCI and 2 control individuals

smoked and 4 SCI individuals used medication, none of which are known to substantially interfere with vascular reactivity (rectal laxantia [n=2], furosemide, and tolterodine). All of the SCI individuals had long-standing traumatic spinal cord injury with a motor and sensory complete spinal cord lesion above T6 (American Spinal Injury Association Impairment Scale A, zone of partial preservation above T6[12]). The level of spinal cord injury was assessed by clinical examination. The study was carried out in accordance with the Declaration of Helsinki and was approved by the medical ethical committee of our institution. All of the subjects gave written informed consent.

Experimental Procedures and Protocol

All of the subjects refrained from caffeine-containing food and beverages, vitamin C supplements, nicotine, and alcohol for >12 hours before the experiment and from heavy physical activity for >24 hours before the experiment. Subjects had been fasting for >12 hours and had emptied their bladder in the hour before the experiment. All of the experiments were performed in the morning in a quiet, temperature-controlled room (23±1°C). Each subject was studied on 2 different occasions, separated by 1 week. On the first experimental day, subjects were screened with a health questionnaire, physical examination, and a resting ECG. Subsequently, a measurement of leg vascular resistance (LVR) in supine rest and during exaggerated sympathetic activity, that is, AD in SCI and a CPT of the hand in control individuals. On the second experimental day, nicardipine, a calcium ion influx inhibitor (calcium channel blocker), and phentolamine, a nonselective competitive antagonist of α-adrenergic receptors, were successively infused into the right femoral artery. LVR was measured during supine rest, as well as during AD in SCI and during a CPT in control individuals.

On both days, subjects were positioned comfortably in a supine position on a bed with an anti-ulcer mattress. Experimental procedures on the first experimental day started after a supine resting period of ≥30 minutes. First, baseline upper leg blood flow was measured for 10 minutes in a supine position, and, subsequently, AD was provoked in SCI individuals for 5 minutes. In control individuals, a CPT of the hand was applied for 3 minutes, during which upper leg blood flow was measured. On the second experimental day, an intra-arterial cannula (Angiocath 16-gauge, Becton Dickinson Infusion Therapy Systems Inc) was introduced after local anesthesia (0.4 mL of 10-mg/mL lidocaine hydrochloride, Fresenius Kabi Nederland BV) using a modified Seldinger technique into the right femoral artery at the level of the inguinal ligament for arterial blood pressure measurement (HP monitor type 78353B, Hewlett Packard GmbH) and intra-arterial drug administration by an automatic syringe infusion pump (Type P2000, IVAC Medical Systems). The measurements started after a supine resting period of ≥30 minutes after cannulation of the right femoral artery. First, baseline upper leg blood flow was measured during a 5-minute saline (0.9% NaCl, Baxter BV) infusion period, followed by nicardipine infusion (1 mg/mL of Cardene, Astellas Pharma BV) for 10 minutes in a dose of 0.5 μg/min per 100 mL of leg volume.[13,14] In a pilot study, higher doses of nicardipine did not further increase blood flow in a control individual. In the last 5 minutes of nicardipine infusion, AD was provoked in SCI and a CPT in control individuals. After a resting period of ≥30 minutes with only saline infusion, the same protocol was performed but this time with phentolamine infusion (10 mg/mL of Regitine, Novartis Pharma BV) in a dose of 12 μg/min of 100 mL of leg volume.[15] Nicardipine was infused first because of the short half-life time of 2 to 5 minutes,[16] in contrast to the unclear half-life time of phentolamine. The schedule of the protocol is shown in Figure 1.

AD in SCI individuals was provoked by inflating a blood pressure cuff to 220 mm Hg on the contralateral upper leg, which gives a nociceptive stimulus.[2,3] According to the literature, AD was achieved when there was a systolic blood pressure response to the stimulus of ≥20 mm Hg[3,17,18] or a 20% increase in blood pressure with visualized vasoconstriction.[4] On the first experimental day we attempted to provoke AD with different stimuli (bladder percussion, CPT of the foot, and inflating a blood pressure cuff) to see which stimulus would
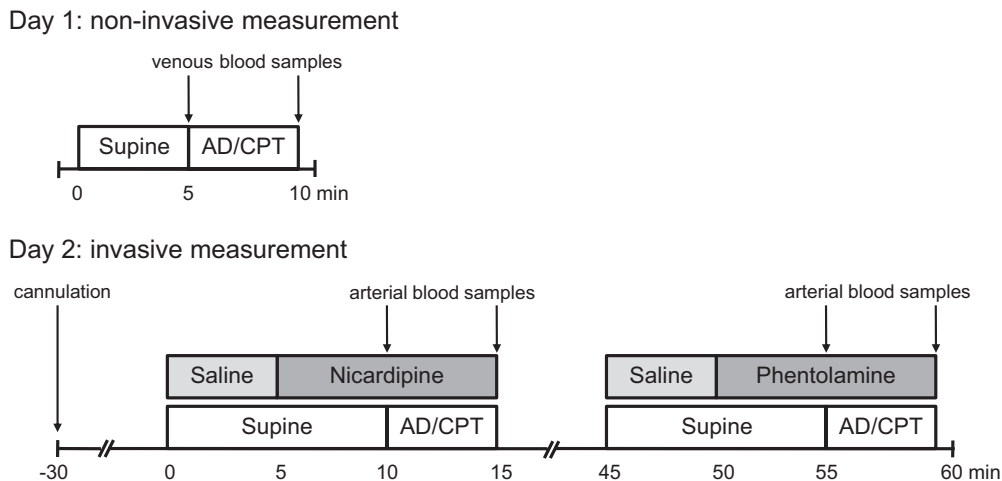
Day 1: non-invasive measurement

Day 2: invasive measurement

Figure 1. Schematic representation of the experimental protocol. AD indicates autonomic dysreflexia in SCI individuals. CPT indicates cold pressor test of the hand in control individuals. Saline, NaCl 0.9%; nicardipine, 0.5 μg/min per 100 mL of leg volume; phentolamine, 12 μg/min per 100 mL of leg volume.

result in the highest increase in blood pressure and fulfill the criteria.[3,4,17,18] Bladder percussion could not be performed in all of the SCI individuals (sacral rhizotomy and electric bladder stimulator), and the frequency and pressure of the bladder percussion was difficult to standardize. A CPT of the foot did not increase mean arterial pressure (MAP) in 5 consecutive SCI individuals and was, therefore, considered an inappropriate stimulus. Inflating a blood pressure cuff to 220 mm Hg on the contralateral leg resulted in the highest increases in blood pressure, was consistent in provoking AD, appeared easy to standardize, and was applicable for each SCI individual. Inflating a blood pressure cuff to 220 mm Hg did not result in hemodynamic changes or in LVR of the contralateral leg in control individuals. We, therefore, decided to use this stimulus to provoke AD in SCI individuals.

To elevate sympathetic activity in control individuals, a CPT of the hand was applied.[19] A CPT consisted of immersion of the right hand into ice-water (4°C) for a period of 3 minutes.[19]

Measurements

Bilateral upper leg blood flow was measured by ECG-triggered venous occlusion plethysmography, using mercury-in-silastic strain gauges (DE Hokanson, Bellevue, WA), and electrically calibrated.[20] In the supine position, the legs were positioned ≈5 cm above heart level to facilitate venous outflow between venous occlusions.[21] Strain gauges were placed 10 cm above the patella, and 12-cm width occlusion cuffs, placed on the thigh above the strain gauge, were inflated with a rapid cuff inflator (DE Hokanson), within 1 second, to 50 mm Hg.[22] Occlusion pressures were sustained for 8 heart cycles, after which the cuff was deflated instantaneously (for 10 heart cycles).

Arterial blood pressure was measured continuously using a non-invasive blood pressure device (Portapres, TNO) on day 1. A finger cuff was attached to the middle phalanx of the left third finger to measure finger arterial blood pressure, which accurately reflects intra-arterial blood pressure changes.[23] On day 2, arterial blood pressure was continuously measured intra-arterially using the femoral artery cannula. MAP values were derived beat to beat, and heart rate was the inverse of the interbeat interval.

Leg volume was determined by anthropometry, as described and validated by Jones and Pearson.[24]

Venous (day 1) and arterial (day 2) blood samples were taken to determine norepinephrine levels in SCI and control individuals. In SCI individuals, renin and angiotensin II levels were determined as well to establish a possible role of the renin-angiotensin system in AD. The blood samples were taken at rest, before infusion of nicardipine and phentolamine, and directly after AD in SCI and after a CPT in control individuals (Figure 1). The samples were collected in prechilled glass tubes on melting ice containing glutathione and EDTA for determination of norepinephrine levels and nonchilled glass tubes for determination of renin and angiotensin II levels. Samples were processed immediately in a refrigerated centrifuge and stored at −80°C until further analysis. Plasma norepinephrine was measured by sensitive and specific high-performance liquid chromatography with fluorometric detection, as described previously.[25] Plasma renin was measured by immunoradiometric assay provided by CISbio International, and angiotensin II levels in medium were measured by radioimmunoassay (detection limit: 0.5 pmol/L) as described previously.[26]

Data Analysis

A data acquisition system digitalized the data with a sample frequency of 100 Hz (Medical Information Data Acquisition, Instrumentation Department, Radboud University Nijmegen Medical Centre). Upper leg blood flow was calculated as the slope of the volume change over a 4-second interval using a customized computer program (MATLAB 6.1, Mathworks). MAP and heart rate values over the same intervals were averaged.

LVR was calculated as the arterial-venous pressure gradient divided by upper leg blood flow. For these calculations, we assumed that central venous pressure was 9 mm Hg in a supine position.[27] During AD and during a CPT, the average of the highest 3 consecutive measurements was taken to determine LVR.

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 (SPSS) software. Data are presented as mean±SD unless otherwise stated. The level of statistical significance was set at $\alpha=0.05$. To assess differences in baseline values between SCI and control individuals, unpaired t tests were used. Repeated-measures ANOVAs were used to assess the effect of AD within the SCI group and of a CPT within the control group on the first day and the effect of infusion of nicardipine or phentolamine on the second day. Post hoc t tests were performed when the ANOVA reported a significant main or interaction effect. Bonferroni correction was used to correct for multiple comparisons.

Results

Baseline Values

Supine resting systolic blood pressure and MAP in SCI were lower ($P=0.02$) and LVR was higher ($P<0.01$) compared with control individuals. Provoking AD in SCI and performing a CPT in control individuals on day 1 resulted in an

Table 2. Systemic Hemodynamic Variables and LVR Reactions During AD in SCI Individuals and CPT in Control Individuals Without and With Phentolamine or Nicardipine Infusion

Intervention	SCI Individuals (n=6)			Control Individuals (n=7)		
	MAP, mm Hg	HR, bpm	LVR, AU	MAP, mm Hg	HR, bpm	LVR, AU
Baseline	82±6	55±7	32.7±3.1	96±6‡	57±6	22.3±6.6‡
AD/CPT	103±8*	52±6	56.3±13.8*	112±14*	59±6	40.1±17.8*
Phentolamine infusion						
Saline	77±9	51±10	23.8±7.2	90±13	61±7	21.9±5.7
Phentolamine	75±12	54±10	18.9±6.2*	86±11	66±8*	12.4±1.9*
AD/CPT	84±11	53±10	26.9±8.2†	91±3	68±4	13.1±2.5
Nicardipine infusion						
Saline	79±10	53±11	23.6±6.3	86±12	57±7	19.8±5.5
Nicardipine	78±11	53±11	21.3±6.0	85±11	62±8*	13.8±4.1*
AD/CPT	90±11†	51±10	36.4±15.5†	94±13†	65±4	18.1±7.3†

Values represent mean±SD. HR indicates heart rate.

*Data are significantly different from baseline or saline.

†Data are significantly different from nicardipine or phentolamine.

‡Data are significantly different from SCI individuals.

increase in MAP ($P<0.01$ and $P=0.01$, respectively) and LVR ($P<0.01$ and $P=0.01$, respectively), whereas heart rate did not change in either group. The LVR increase during AD in SCI was similar to the increase during a CPT in control individuals (Tables 1 through 3 and Figure 2).

Phentolamine and Nicardipine Infusion During AD in SCI Individuals

LVR in SCI individuals was lower ($P=0.02$) during saline infusion on day 2 compared with the baseline value on day 1.

Infusion of phentolamine did not change MAP and heart rate but did lower LVR ($P=0.04$). Provoking AD during phentolamine infusion did not change MAP and heart rate; however, LVR increased ($P=0.02$). The increase in LVR was significantly lower ($P=0.04$) during phentolamine infusion (8.0±4.5 arbitrary units [AU]) compared with the LVR increase on day 1 (23.6±13.4 AU). Nicardipine infusion did not change MAP, heart rate, or LVR. Provoking AD during nicardipine infusion resulted in an increase in MAP ($P=0.03$) and LVR ($P=0.04$) with no change in heart rate. The increase

Table 3. Individual Increase in MAP and LVR During AD in SCI Individuals and CPT in Control Individuals Without and With Phentolamine or Nicardipine Infusion

Subject	Day 1		Phentolamine Infusion		Nicardipine Infusion	
	Δ MAP, mm Hg (%)	Δ LVR, AU (%)	Δ MAP, mm Hg (%)	Δ LVR, AU (%)	Δ MAP, mm Hg (%)	Δ LVR, AU (%)
SCI during AD						
SCI1	12 (13)	4 (13)	2 (2)	14 (87)	8 (8)	9 (57)
SCI2	15 (16)	43 (142)	4 (4)	3 (16)	9 (10)	9 (50)
SCI3	33 (44)	20 (54)	8 (12)	9 (30)	17 (25)	21 (72)
SCI4	6 (8)	19 (67)	1 (2)	10 (64)	4 (5)	24 (101)
SCI5	30 (40)	33 (95)	36 (58)	11 (58)	27 (39)	25 (98)
SCI6	29 (36)	22 (67)	3 (4)	3 (14)	8 (11)	2 (12)
SCI (n=6)	21±11 (26±15)	24±13 (73±40)	9±13* (14±22)	8±5* (45±27)	12±8* (16±13)	15±9† (65±30)
Control during CPT						
C1	4 (5)	7 (51)	8 (10)	1 (9)	13 (16)	11 (58)
C2	14 (15)	8 (54)	−15 (−14)	−3 (−23)	13 (12)	5 (27)
C3	9 (9)	12 (41)	6 (7)	3 (26)	3 (4)	1 (13)
C4	6 (6)	14 (54)	10 (13)	2 (19)	−2 (−3)	1 (8)
C5	15 (15)	17 (58)	6 (7)	0 (3)	6 (7)	1 (10)
C6	34 (36)	47 (175)	14 (19)	0 (3)	16 (21)	10 (82)
C7	31 (32)	21 (110)	7 (9)	0 (4)	13 (16)	1 (14)
Control (n=7)	16±12 (17±12)	18±13 (78±45)	5±9* (7±10)	1±2* (6±14)	9±6* (10±8)	4±4* (30±26)

Values represent mean±SD. Δ indicates increase; %, percentage increase; C, control subject.

*Data are significantly different from day 1.

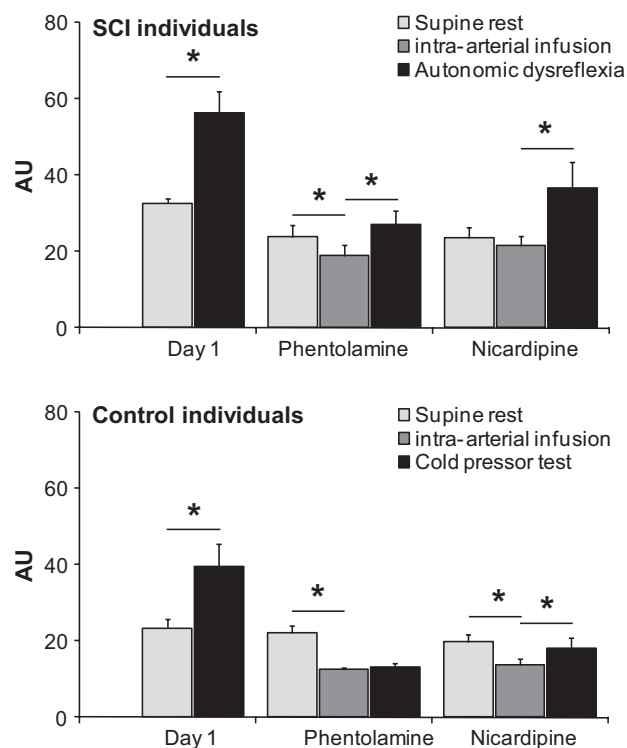†Data are significantly different from phentolamine infusion.

Figure 2. LVR in SCI individuals (n=6, top graph) and control individuals (n=7, bottom graph). During supine rest, infusion of phentolamine and nicardipine and during autonomic dysreflexia in SCI and CPT in control individuals with and without infusion. Values represent mean+SE. *Significant difference.

Table 4. Norepinephrine, Renin, and Angiotensin II Levels at Baseline and During AD in SCI Individuals and a CPT in Control Individuals Without and With Phentolamine or Nicardipine Infusion

Intervention	SCI Individuals (n=6)			Control (n=7), NE, nmol/L
	NE, nmol/L	Renin, mE/L	AT II, pmol/L	
Baseline	0.66±0.31	10±5	1.96±1.00	1.09±0.18†
AD/CPT	0.93±0.21	10±7	2.02±1.38	1.93±0.71*†
Phentolamine infusion				
Saline	0.76±0.74	9±4	1.20±0.32	1.14±0.29
AD/CPT	1.49±1.44*	9±4	1.46±0.58	3.22±1.11*
Nicardipine infusion				
Saline	0.60±0.60	7±5	1.34±0.65	0.90±0.15
AD/CPT	1.00±0.92*	7±5	0.96±0.47	1.67±0.41*

Values represent mean±SD. Control, control individuals; NE, norepinephrine; AT II, angiotensin II; AD/CPT, autonomic dysreflexia in SCI individuals or CPT in control individuals.

*Data are significantly different from baseline or saline.

†Data are significantly different from SCI individuals.

in MAP during AD was significantly lower ($P=0.03$) during nicardipine infusion (11.9±8.4 mm Hg) compared with the MAP increase on day 1 (21.3±10.9 mm Hg). Nicardipine did not significantly attenuate the LVR increase during AD ($P=0.12$), whereas the LVR increase provoked by AD was significantly lower ($P<0.05$) during phentolamine (8.0±4.5 AU) compared with nicardipine infusion (15.1±9.9 AU). In the noninfused leg, no change in LVR was seen during infusion of phentolamine (31.3±10.3 versus 30.0±10.0 AU) or during nicardipine (33.0±15.8 versus 33.8±16.8 AU; Tables 2 and 3 and Figure 2).

Phentolamine and Nicardipine During CPT in Control Individuals

Phentolamine infusion in control individuals did not change MAP but did increase heart rate ($P=0.02$) and resulted in a decrease in LVR ($P=0.01$). Phentolamine infusion completely abolished the LVR increase in response to a CPT without affecting MAP or heart rate. Infusion of nicardipine did not change MAP but increased heart rate ($P=0.02$) and decreased LVR ($P<0.05$) in control individuals. A CPT during nicardipine infusion increased MAP and LVR ($P=0.04$ and $P=0.03$, respectively) with no change in heart rate. The MAP and LVR increase were significantly less pronounced ($P=0.04$ and $P=0.03$, respectively) during nicardipine infusion compared with day 1. In the noninfused leg, no change in LVR was seen during phentolamine infusion (23.0±8.6 versus 21.1±8.0 AU), and the LVR increase during a CPT to 27.2±11.9 AU was lower compared

with day 1, probably because of spillover of phentolamine to the noninfused leg. LVR in the noninfused leg did not change during nicardipine infusion (21.1±7.6 versus 21.8±8.0 AU), and during a CPT, the LVR increased (37.2±16.0 AU) similar to day 1 (Tables 2 and 3 and Figure 2).

Blood Samples

Baseline norepinephrine levels were significantly lower ($P<0.01$) in SCI compared with control individuals. During AD, norepinephrine did not significantly increase in SCI in contrast to control individuals during a CPT ($P=0.01$). Norepinephrine increased significantly during AD, in combination with phentolamine and nicardipine infusion in SCI ($P=0.04$ and $P=0.03$, respectively) and during a CPT in control individuals ($P<0.01$, both conditions). The increase in norepinephrine during phentolamine infusion was significantly more pronounced ($P=0.04$) in control than in SCI individuals. There were no significant increases in renin and angiotensin II levels during AD in SCI individuals without or with phentolamine or nicardipine infusion (Table 4).

Discussion

The major finding of this study is that AD in SCI individuals is not entirely mediated through the α-adrenergic pathway, indicated by the presence of a remaining residual leg vasoconstrictor response during AD in SCI individuals during phentolamine infusion. Nevertheless, a more pronounced attenuation of the LVR increase during AD was present during phentolamine infusion compared with a nicardipine infusion. In contrast to SCI individuals, phentolamine infusion completely abolished the vasoconstriction response to a CPT in control individuals, which could indicate that the presence of supraspinal sympathetic control in control individuals may suppress the role of nonadrenergic transmission during exaggerated sympathetic activity.

Contribution of Nonadrenergic Transmission

The LVR increase during AD in SCI individuals did not differ from the LVR increase during a CPT in control individuals. Nevertheless, phentolamine completely abolished the LVR increase in control individuals during a CPT, whereas a significant residual leg vasoconstrictor response occurred in SCI individuals during AD with phentolamine infusion. These results suggest that nonadrenergic transmission contributes to the leg vasoconstriction during exaggerated sympathetic activity in SCI but not in control individuals. This interpretation is supported by the more pronounced increase in plasma norepinephrine levels in control individuals compared with SCI individuals in response to exaggerated sympathetic activity. This observation challenges the widespread view that the vasoconstrictor response during AD in SCI individuals is entirely α-adrenergic mediated.[2–4,28]

Because phentolamine is a nonselective competitive α-adrenoceptor antagonist, incomplete α-adrenoceptor blockade could, in theory, explain the residual LVR increase in SCI individuals. A similar intra-arterial dose of phentolamine has been used previously and achieved a maximal vasodilator effect in both SCI and control individuals, indicating complete α-adrenoceptor blockade.[15,29,30] Moreover, the LVR increase during a CPT in control individuals was completely abolished during phentolamine infusion, despite a larger increase in plasma norepinephrine compared with SCI individuals. This confirms that intra-arterial infusion of phentolamine achieved effective intrasynaptic drug concentrations[30] and excludes incomplete α-adrenergic blockade as an explanation for the residual vasoconstrictor response in SCI individuals in the present study.

Because vasoconstriction during AD occurs rapidly, it is not likely that other vasoconstrictor mechanisms play an important role, such as the renin-angiotensin system. The renin-angiotensin system is a slow-acting vasoconstriction mechanism and, therefore, unlikely to cause immediate arterial vasoconstriction on a visceral, noxious, or nociceptive stimulus. Moreover, there were no increases in renin and angiotensin II levels during AD in SCI individuals, supporting the notion that there was no activation of the renin-angiotensin system. However, the local angiotensin system could still play a role, because we did not have an additional angiotensin II subtype I receptor blockade. It is unlikely that vasopressin plays a role, because vasopressin levels are low in SCI individuals and do not increase during AD.[31] The instant reaction to the triggering stimulus provoking AD in combination with the lack of supraspinal control in SCI individuals causing exaggerated sympathetic activity provides enough evidence for a sympathetic-mediated mechanism. Because α-adrenoceptor blockade did not abolish the LVR increase during AD, other sympathetic neurotransmitters might be involved, such as ATP and neuropeptide Y.[10] ATP, neuropeptide Y, and norepinephrine are costored in the sympathetic synapse and are simultaneously released.[32] Receptors for these neurotransmitters are located on smooth muscle and endothelial cells of blood vessels.[32] It is thought that norepinephrine and ATP have a coordinated action in neurogenic vasoconstriction, which is modulated by neuropeptide Y.[32] We did not investigate the mechanism by which spinal cord injury increases sympathetic nonadrenergic transmission. Because the sympathetic nervous system below the lesion in SCI individuals is without central inhibitory pathways,[2,3] in contrast to control individuals, we speculate that an intact supraspinal control of sympathetic outflow preferentially suppresses sympathetic nonadrenergic transmission. Alternatively, spinal cord injury alters the relative concentrations of costored neurotransmitters. In this regard, an intermediate role for endothelin is worth mentioning. We have shown previously that the contribution of endothelin in LVR is increased in SCI individuals.[33] In rats, endothelin 1 infusion increased the relative contribution of ATP as a functional sympathetic neurotransmitter.[34] Therefore, endothelin may mediate the increased contribution of nonadrenergic neurogenic vasoconstriction in SCI individuals.

Phentolamine Effect Superior to Nicardipine

Provoking AD in SCI individuals during nicardipine infusion still resulted in an LVR increase with a concurrent increase in MAP. However, the MAP increase with nicardipine infusion was lower compared with day 1, indicating an attenuation of the blood pressure response during AD in SCI individuals. This is consistent with 1 previous study demonstrating a lower blood pressure response during oral nifedipine pretreatment in SCI individuals who exhibited AD during electroejaculation.[11] However, the LVR increase was similar to day 1, indicating a minor effect of nicardipine on leg vasoconstriction.

Despite the residual LVR increase during AD in SCI individuals with phentolamine infusion, this LVR increase was significantly lower than with nicardipine infusion, and, moreover, with phentolamine there was no change in MAP. These results indicate a superior effect of an α-adrenoceptor antagonist compared with a calcium channel blocker on leg vasoconstriction and concurrent blood pressure response during AD in SCI individuals.

An obvious explanation for the observed difference in effect could be an inefficient dosage of nicardipine. Infusion of nicardipine did not result in a significant decrease in basal LVR in SCI individuals. However, in control individuals, basal LVR decreased with the same dose, and, in a pilot study, higher dosages of nicardipine did not result in a more pronounced vasodilatory effect. We are, therefore, convinced that we used a sufficient dose of nicardipine. The vasodilatation caused by nicardipine is, however, more pronounced in hypertensive compared with normotensive individuals.[16] Because blood pressure in SCI individuals was lower compared with control individuals, the effect of nicardipine on LVR could be smaller for this reason.

Baseline Values

Consistent with our results, SCI individuals with a high spinal cord lesion are prone to low resting blood pressures,[1–3] which is thought to be attributed to a diminution in sympathetic nervous activity below the lesion as supported by low plasma norepinephrine levels.[1,2] Although the reduced norepinephrine levels in SCI individuals may also be influenced by the efficiency of the reuptake by the norepinephrine transporter and changes in blood flow redistribution caused by inactivity and muscle atrophy. Despite lower sympathetic activity, SCI

individuals have a higher resting LVR,[15,30,35] probably because of a combination of functional[33] and structural vascular changes.[36] During AD, SCI individuals can increase their LVR to the same extent as control individuals during a CPT. Although a CPT is not directly comparable with AD, both are strong sympathetic stimuli, notwithstanding the physiological and neurological differences, especially the absence (SCI) or presence (control) of supraspinal control.[2,3]

Limitations

Although α-adrenergic responsiveness deteriorates with age,[37,38] all of the SCI and control individuals demonstrated similar increases in LVR during AD and a CPT, respectively, compared with their peers. Moreover, the oldest control individual (C7, 54 years) had a complete abolished LVR increase during a CPT with phentolamine infusion, and the oldest SCI individual (SCI3, 69 years) had an attenuated LVR increase during AD with phentolamine infusion.

Infusion of saline in SCI individuals lowered supine LVR compared with day 1. This is probably because of a more pronounced reaction to an increase in shear on the vascular wall, caused by the saline infusion, because of functional changes in SCI individuals.[33] The noninfused leg did not demonstrate a lower supine LVR, indicating that the lower supine LVR in the infused leg is probably caused by the saline infusion. The lower supine LVR did not have any effect on MAP and heart rate. Because the focus of the study was the effect of phentolamine and nicardipine infusion on the LVR increase during AD and a CPT, we may assume that the lower basal LVR did not influence our results.

Perspectives

The management of AD in SCI individuals remains a challenge in clinical practice.[18,39] Over the years, many different antihypertensive agents have been used.[4,18] In earlier days, α-adrenoceptor antagonists were used[4]; however, their use was limited, and nowadays nifedipine (calcium channel blocker) is used as a primary agent in the management of AD.[4] However, the present study demonstrates that an α-adrenoceptor antagonist appears to have a more pronounced effect than a calcium channel blocker on the LVR and concurrent MAP increase during AD in SCI individuals. Moreover, serious adverse reactions after the use of immediate-release nifedipine in hypertensive emergencies in non-SCI individuals have been reported.[40] The present study demonstrates that AD in SCI individuals is not entirely α-adrenergic mediated and that sympathetic nonadrenergic transmission may partly explain the LVR increase. The development of antagonists of nonadrenergic transmitters may be a target for future AD management in SCI individuals. Perhaps these antagonists may reduce the blood pressure increase during AD without lowering the blood pressure in the absence of AD.

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