Autonomic dysreflexia during sperm retrieval in spinal cord injury: influence of lesion level and sildenafil citrate

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Sheel, A. William, Andrei V. Krassioukov, J. Timothy Inglis, and Stacy L. Elliott. Autonomic dysreflexia during sperm retrieval in spinal cord injury: influence of lesion level and sildenafil citrate. J Appl Physiol 99: 53–58, 2005. First published March 24, 2005; doi:10.1152/japplphysiol.00154.2005.—Autonomic dysreflexia (AD) can occur during penile vibratory stimulation in men with spinal cord injury, but this is variable, and the association with lesion level is unclear. The purpose of this study was to characterize the cardiovascular responses to penile vibratory stimulation in men with spinal cord injury. We hypothesized that those with cervical injuries would demonstrate a greater degree of AD compared with men with thoracic injuries. We also questioned whether the rise in blood pressure could be attenuated by sildenafil citrate. Participants were classified as having cervical (n = 8) or thoracic (n = 5) injuries. While in a supine position, subjects were instrumented with an ECG, and arterial blood pressure was determined beat by beat. Subjects reported to the laboratory twice and received an oral dose of sildenafil citrate (25–100 mg) or no medication. Penile vibratory stimulation was performed using a handheld vibrator to the point of ejaculation. At ejaculation during the nonmedicated trials, the cervical group had a significant decrease in heart rate (−5–10 beats/min) and increase in mean arterial blood pressure (+70–90 mmHg) relative to resting conditions, whereas the thoracic group had significant increases in both heart rate (+8–15 beats/min) and mean arterial pressure (+25–30 mmHg). Sildenafil citrate had no effect on the change in heart rate or mean arterial pressure in either group. In summary, men with cervical injuries had more pronounced AD during penile vibratory stimulation than men with thoracic injuries. Administration of sildenafil citrate had no effect on heart rate or blood pressure during penile vibratory stimulation in men with spinal cord injury.

arterial pressure; cardiovascular; penile vibratory stimulation; sympathetic nervous system

Ejaculatory dysfunctions are an uncommon cause of male infertility in the general population (8). However, spinal cord injury (SCI) commonly affects men in their reproductive years during which many men experience fertility-related problems, including erectile and ejaculatory dysfunction, impaired spermatogenesis, abnormal sperm (viability, motility, and morphology), genitourinary infection, and endocrine abnormalities (26). The recent development and refinement of penile vibratory stimulation (PVS) and electroejaculation (EEJ) has enhanced the treatment of ejaculatory dysfunction in SCI (26). The physiology of ejaculation is complex and is a highly coordinated effort involving the brain, spinal cord, sympathetic and parasympathetic nervous system, as well as efferent and afferent components of the peripheral nervous system. In short, the goal of PVS is to activate the ejaculatory reflex in the thoracolumbar area of the spinal cord. It is generally believed that PVS requires an intact spinal cord at the level of T11–S4 to cause antegrade ejaculation (4, 5, 28). However, it is not clear how the level and completeness of the SCI lesion accurately predict successful ejaculation (4, 28).

The cardiovascular responses to genital stimulation and ejaculation in noninjured men are well known and involve a general autonomic response consisting of increased systolic (SBP) and diastolic blood pressure (DBP) and increased heart rate (HR), which all peak at ejaculation and immediately return to baseline after it (17, 19, 23). However, significant dysfunction of the sympathetic nervous system is associated with SCI, particularly at higher levels of SCI, and cardiovascular deficits can be present (15, 20). One of them is autonomic dysreflexia (AD), which is characterized by episodic hypertension in response to noxious or nonnoxious stimuli below the level of the injury and is usually restricted to those with a lesion level at or above T6. In addition to a sudden rise in blood pressure, AD is often accompanied by symptoms such as headaches, anxiety, sweating, and bradycardia (14, 20, 29). There are reports of AD during PVS and EEJ in men with SCI (7, 10, 12, 22, 27). However, from the available data, the presence of AD appears variable, and the predictability of AD occurrence with lesion level is not well described. As such, the primary purpose of our study was to characterize the cardiovascular responses to PVS in men with different lesion levels and severity of injury. We hypothesized that those with cervical injuries would demonstrate a greater degree of AD in response to PVS compared with men with thoracic injuries based on the higher degree of sympathetic nervous system disturbance expected at the higher lesion level. We also questioned whether the disproportionate rise in blood pressure during PVS in men with SCI could be altered with use of pharmacological agents. Therapeutic measures to reduce arterial blood pressure during EEJ in men with SCI include the use of oral nifedipine (27) and intravenous infusions of prostaglandin E2 (10). There is some evidence that, in patients with Parkinson’s disease, and those with multiple system atrophy, orally administered sildenafil citrate (i.e., Viagra) has a hypotensive effect on mean blood pressure in the lying, sitting, and standing positions (12). Sildenafil citrate is a highly selective inhibitor of phosphodiesterase type 5 (PDE5), which is used as an effective treatment of erectile dysfunction (31) and has been shown to decrease resting blood pressure; cardiovascular; penile vibratory stimulation; sympathetic nervous system

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pressure in healthy volunteers (12). However, to our knowledge, administration of sildenafil citrate and its potential role in reducing arterial blood pressure during PVS in men with SCI have not been systematically investigated. Therefore, our secondary purpose was to determine whether sildenafil citrate would attenuate the rise in blood pressure that can accompany PVS in men with SCI.

METHODS

Participants. All experimental procedures and protocols were approved by the Clinical Screening Committee for Research of the University of British Columbia. A total of 13 men participated in this study after providing informed, written consent. Before experimentation, subjects underwent neurological assessment and anthropometric measurements. The level and severity of SCI were determined by assessment of motor and sensory impairment according to the American Spinal Injury Association (ASIA) scoring system by a qualified physician. The ASIA Grade A represents the most severe SCI with complete motor and sensory impairment, and ASIA Grade D characterizes minor SCI (incomplete and mild motor dysfunction) (21).

Level and completeness of the lesions were assessed using the American Spinal Injury Association (ASIA) scale (21).

Level and severity of spinal cord injury in study subjects

<table>
<thead>
<tr>
<th>Subject No</th>
<th>Injury Level</th>
<th>ASIA Score</th>
<th>Time Since Injury, mo</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>C3</td>
<td>A</td>
<td>187</td>
</tr>
<tr>
<td>2</td>
<td>C4</td>
<td>A</td>
<td>194</td>
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<tr>
<td>3</td>
<td>C5</td>
<td>A</td>
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<td>4</td>
<td>C6</td>
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<td>73</td>
</tr>
<tr>
<td>5</td>
<td>C7</td>
<td>B</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>C8</td>
<td>B</td>
<td>285</td>
</tr>
<tr>
<td>7</td>
<td>C9</td>
<td>B</td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>C10</td>
<td>C</td>
<td>115</td>
</tr>
<tr>
<td>9</td>
<td>T1</td>
<td>A</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>T2</td>
<td>A</td>
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</tr>
<tr>
<td>11</td>
<td>T3</td>
<td>A</td>
<td>191</td>
</tr>
<tr>
<td>12</td>
<td>T4</td>
<td>A</td>
<td>257</td>
</tr>
<tr>
<td>13</td>
<td>T5</td>
<td>C</td>
<td>239</td>
</tr>
</tbody>
</table>

RESULTS

Subject characteristics and baseline cardiovascular parameters. Individual subject injury characteristics are shown in Table 1. The cervical group had injuries ranging from C2 to C7 and was classified as ASIA A (n = 3), B (n = 4), or C (n = 1). The thoracic group had injuries at T3–T6 and was categorized as ASIA A (n = 4) or C (n = 1). Mean descriptive subject characteristics are shown in Table 2. The groups were not statistically different for age, height, weight, body mass index, or time since injury (P > 0.05). Under resting control conditions HR, DBP, and MAP were similar between the cervical and thoracic groups (Table 3; P > 0.05). Control resting SBP was lower in individuals with cervical SCI relative to thoracic (P < 0.05). Administration of sildenafil citrate had no effect on resting HR in either group. Relative to the thoracic group, subjects with cervical injuries had a lower resting SBP, DBP, and MAP during the sildenafil citrate trial (P < 0.05). Compared with control conditions, sildenafil citrate caused a statistically lower DBP and MAP in the cervical group and a lower DBP in the thoracic group (P < 0.05).

Cardiovascular values at ejaculation. Figure 1 shows a beat-by-beat recording from one subject with a cervical injury for arterial blood pressure and HR during PVS and at ejaculation. In response to PVS and ejaculation in this subject, there was a significant rise in both SBP and DBP relative to rest, whereas HR was reduced relative to rest in control conditions. Mean values for HR and blood pressure measures at ejaculation are shown in Table 4. During control experiments, absolute values for HR tended to be lower at ejaculation in the cervical group relative to the thoracic group, but this was variable and did not reach statistical significance (P = 0.06). The blood pressure response at ejaculation was different between groups where SBP, DBP, and MAP were higher in the cervical group compared with the thoracic group (P < 0.05).

Table 1. Level and severity of spinal cord injury in study subjects

Table 2. Mean subject characteristics

Group | Time Since Injury, mo | Age, yr | Height, cm | Mass, kg | Body Mass Index, kg/m² |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Cervical</td>
<td>135±30</td>
<td>32±2</td>
<td>161±2</td>
<td>73.6±3.3</td>
<td>28.4±1.5</td>
</tr>
<tr>
<td>Thoracic</td>
<td>167±38</td>
<td>35±3</td>
<td>160±2</td>
<td>76.4±4.1</td>
<td>29.8±2.0</td>
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</table>
There was no effect of sildenafil citrate on cardiovascular variables at ejaculation ($P > 0.05$). Figure 2 shows the cardiovascular response to ejaculation in relative terms. The cervical group demonstrated a reduction in HR relative to rest, whereas the thoracic group demonstrated a modest rise in HR. There was no effect of sildenafil citrate. Values for blood pressure (SBP, DBP, and MAP) were significantly higher in the cervical group compared with the thoracic group ($P < 0.05$), and there was no effect of sildenafil citrate ($P > 0.05$).

**DISCUSSION**

This is the first study to systematically characterize the cardiovascular responses to PVS with and without sildenafil citrate in men with different SCI lesion levels. The principal findings of this investigation are threefold. First, we have demonstrated that in men with SCI there is profound AD during sperm retrieval that is dependent on lesion level. Specifically, men with cervical injuries demonstrated greater AD compared with men with thoracic injuries. Second, we have shown that sildenafil citrate has no effect on the cardiovascular responses to PVS and ejaculation in men with SCI. Third, we observed that resting blood pressure in the cervical group was lower than in the thoracic group and that administration of sildenafil citrate significantly decreased resting blood pressure in the cervical group but not the thoracic group.

**Autonomic dysreflexia.** Mortality and morbidity of people with SCI have decreased, and their life expectancy has approached that of able-bodied individuals (18). As with a growing fraction of the able-bodied population, cardiovascular disease is now one of the leading causes of death in those with SCI (18). Normal sexual function has become an important consideration for the management of the SCI patient. In a recent large survey of SCI individuals (681 participants; 51% quadriplegic individuals and 49% paraplegic individuals), the importance of sexual function was underscored where both quadriplegic and paraplegic individuals shared similar priorities when ranking bladder and bowel control and sexual function as the first and second important factor affecting quality of life (1). However, as we have shown in the present study, assisted reproductive technologies such as PVS in men with SCI can be accompanied by AD. Our findings demonstrate profound AD in men with cervical injuries and that AD is also present, but to a lesser degree, in men with thoracic injuries (see Fig. 2). The HR and blood pressure response to PVS was variable in the thoracic group where some subjects did not demonstrate AD but rather had a response that was similar to what would be predicted for an able-bodied person. We found that, relative to rest, HR was reduced ($-5$–$-10$ beats/min) in the cervical group at ejaculation. This was accompanied by large increases in SBP ($+90$–$+115$ mmHg), DBP ($+70$–$+80$ mmHg), and MAP ($+70$–$+90$ mmHg), and there was no effect of sildenafil citrate. In the thoracic group, there was a modest rise in HR ($+8$–$+15$ beats/min), SBP ($+35$–$+40$ mmHg), DBP ($+25$–$+30$ mmHg), and MAP ($+25$–$+30$ mmHg), and there was also no sildenafil citrate effect. The typical able-bodied response to sexual arousal and ejaculation in young men involves increases in HR, SBP, DBP, and MAP, which are accompanied by increases in circulating catecholamines. These values can vary depending on the sexual activity and degree of arousal (7,

<table>
<thead>
<tr>
<th>Group</th>
<th>Control HR, beats/min</th>
<th>Control SBP, mmHg</th>
<th>Control DBP, mmHg</th>
<th>Control MAP, mmHg</th>
<th>Sildenafil Citrate HR, beats/min</th>
<th>Sildenafil Citrate SBP, mmHg</th>
<th>Sildenafil Citrate DBP, mmHg</th>
<th>Sildenafil Citrate MAP, mmHg</th>
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</thead>
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<tr>
<td>Cervical</td>
<td>62 ± 4</td>
<td>95 ± 8*</td>
<td>64 ± 5</td>
<td>82 ± 7</td>
<td>61 ± 3</td>
<td>75 ± 7†</td>
<td>44 ± 4†</td>
<td>54 ± 5†</td>
</tr>
<tr>
<td>Thoracic</td>
<td>64 ± 5</td>
<td>121 ± 9</td>
<td>72 ± 7</td>
<td>86 ± 8</td>
<td>66 ± 4</td>
<td>115 ± 9</td>
<td>67 ± 6†</td>
<td>83 ± 6</td>
</tr>
</tbody>
</table>

*Values are means ± SE. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure. †Significantly different from thoracic group, $P < 0.05$. †Significantly different from control group, $P < 0.05$.  

Fig. 1. Beat-by-beat recording from one subject (cervical injury; control trial) for heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) responses to penile vibratory stimulation (PVS) and at ejaculation.
Our data are the first to show that the level of injury affects the degree of AD during PVS where more pronounced AD was present in higher level injuries.

SCI disturbs blood pressure control, which typically depends on supraspinal regulation of sympathetic preganglionic neurons (11). Reflexes within the spinal circuits generally contribute minimally to cardiovascular control in intact humans and animals. After SCI, central nervous system regulation of arterial pressure is dominated by spinal reflex control of these neurons, and the unchecked reflexes can lead to AD (16). Specific AD mechanisms include 1) sympathetic hyperactivity in the isolated spinal cord due to loss of tonic central inhibitor inputs, 2) plastic changes within spinal autonomic circuits, 3) impaired baroreceptor reflex function, and 4) α-adrenoreceptor hyperresponsiveness (29).

It was shown previously that resting arterial blood pressure in individuals with SCI is lower than in able-bodied subjects, with disabling episodes of orthostatic hypotension (6, 20). Despite the lower blood pressure, life-threatening episodes of hypertension, known as AD, may occur, where SBP can reach up to 300 mmHg, potentially leading to stroke and death (9, 20, 29). These cardiovascular abnormalities are attributed to autonomic instability caused by a combination of changes occurring within the spinal autonomic circuits in acute and chronic stages after SCI (20, 29). AD is usually induced by activation of sensory input entering the spinal cord below the level of the lesion. Bladder or colorectal distension and urinary tract infections are among the most common causes of this condition (29). No subjects in the present study had a urinary tract infection.

Because PVS to the point of ejaculation triggers an increase in arterial blood pressure, baroreceptors activate the vagus to depress HR. Bradycardia is therefore present, but, because blood pressure can only be modulated above the lesion after SCI, bradycardia persists (7). Our observations of hypertension and bradycardia are consistent with other findings of AD during PVS in men with SCI (7), and the AD seen in the cervical group may have been partly due to dysfunction in the baroreceptor reflex pathway. However, because we did not directly test this hypothesis, we cautiously make this statement. Sympathetic hyperactivity and α-adrenoreceptor hyperresponsiveness may have also played a mechanistic role in the AD observed, and it is not known what the relative contributions are (29).

Sildenafil citrate. Sildenafil citrate is a selective inhibitor of the enzyme PDE5 (2), which is found predominantly in the corpora cavernosa of the penis (3) and also has vasodilator effects on the pulmonary vasculature (25). cGMP is responsible for penile smooth muscle relaxation and erection via the nitric oxide-cGMP mediated relaxation pathway. Inhibition of...

<table>
<thead>
<tr>
<th>Group</th>
<th>Control HR, beats/min</th>
<th>Control SBP, mmHg</th>
<th>Control DBP, mmHg</th>
<th>Control MAP, mmHg</th>
<th>Sildenafil Citrate HR, beats/min</th>
<th>Sildenafil Citrate SBP, mmHg</th>
<th>Sildenafil Citrate DBP, mmHg</th>
<th>Sildenafil Citrate MAP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>52 ± 6</td>
<td>189 ± 14*</td>
<td>135 ± 11*</td>
<td>151 ± 10*</td>
<td>57 ± 6</td>
<td>188 ± 15*</td>
<td>121 ± 9*</td>
<td>143 ± 11*</td>
</tr>
<tr>
<td>Thoracic</td>
<td>77 ± 7</td>
<td>158 ± 17</td>
<td>97 ± 14</td>
<td>114 ± 13</td>
<td>75 ± 7</td>
<td>158 ± 19</td>
<td>104 ± 12</td>
<td>122 ± 14</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Significantly different from thoracic group, P < 0.05. Note: HR was not significantly different between the cervical and thoracic groups, but there was a nonsignificant trend (P = 0.06) for HR to be lower in the cervical group.

Fig. 2. Change in HR, SBP, DBP, and mean arterial blood pressure (MAP) from rest to ejaculation. Values are means ± SE. *Significantly different (P < 0.05). No differences were detected between the control and sildenafil citrate (P > 0.05).
PDE5 allows for enhancement of erection by blocking the degradation of cGMP. In healthy volunteers, a single oral dose of sildenafil citrate (50, 100, and 200 mg) has a significant lowering effect on supine arterial blood pressure (31). The mean decrease in resting SBP and DBP after a dose of 100 mg was 10.2 and 6.8 mmHg, respectively. Although the above-mentioned blood pressure-lowering effects can be considered modest in healthy subjects, they are potentially important to the SCI patient undergoing penile stimulation for two reasons: it may make the resting hypotension associated with cervical injuries symptomatically worse, and it may be protective in blunting the severe increases in blood pressure seen at ejaculation. We observed a significantly lower resting DBP in both the cervical and thoracic groups with administration of sildenafil citrate compared with the control condition. Sildenafil citrate caused resting MAP to be lower in the cervical group but not the thoracic group. As with previous reports (13), we found that sildenafil citrate had no effect on resting HR. The modest and variable hypotensive effects of sildenafil citrate we observed at rest had no effect on arterial blood pressure at ejaculation (see Fig. 2). It appears that sildenafil citrate has no protective effect on the onset of AD in men with SCI undergoing PVS.

Interestingly, administration of sildenafil citrate significantly decreased resting SBP, DBP, and MAP in the cervical group and DBP in the thoracic group (Table 3). Our experimental approach was not designed to address this question. Nonetheless, a significant hypotensive effect of sildenafil citrate was present in the cervical group, which may have implications for blood pressure regulation during orthostatic challenges.

Critique of methods. We used photoelectric plethysmography to measure arterial blood pressure. Although plethysmographic measurements correlate with intra-arterial measurements during experimental manipulations of arterial pressure (24), the absolute values (mmHg) can be variable. Nonetheless, we are confident in the arterial pressure changes (i.e., change in blood pressure from rest; see Fig. 2) we observed for two reasons. First, the blood pressure device we used is advantageous because it employs an automated hydrostatic height correction to compensate for movements of the hand with respect to heart level. Second, we observed no systematic changes in blood pressure during the rest period, which confirms that our baseline values were stable and our approach to compare resting values with peak values was appropriate.

We did not utilize a placebo because the effects of sildenafil citrate are immediately noticeable to the subject. This may have influenced our results, and we cannot completely rule this out. However, given that we did not observe any systematic effect of sildenafil citrate at ejaculation, we do not believe a lack of a placebo condition influences the interpretation of the data.

Summary. Our research design and experimental approach incorporated subjects with cervical and thoracic SCI. We demonstrated that men with cervical injuries have more pronounced AD during penile vibratory stimulation than men with thoracic injuries. Administration of sildenafil citrate has no effect on HR or blood pressure during penile vibratory stimulation in men with SCI in our study. On the basis of our findings, further studies are warranted using a larger sample of subjects with a range of injury levels and severity to provide a comprehensive evaluation of the degree of AD in relation to SCI.

ACKNOWLEDGMENTS

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GRANTS

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