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Original Article

Autonomic dysreflexia in response to pudendal nerve stimulation

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Study design: Pudendal nerve stimulation in complete spinal cord injury (SCI).
Objective: To evaluate the influence of pudendal nerve stimulation on the cardiovascular system in SCI patients in order to assess the underlying neuronal mechanism and the potential risk during stimulation.
Setting: Swiss Paraplegic Center, and University Hospital, Zurich.
Methods: A total of 22 male patients with a complete SCI were divided into two groups according to the level of lesion: group A (C6–T6, $n=15$) and group B (T7–L2, $n=7$). A total of 66 stimulations using biphasic rectangular impulses (0.2 ms, 10 Hz) with intensities up to 100 mA were applied to the dorsal penile nerve. Of these, 15 stimulations in five patients were repeated after intravenous application of 7 mg of phentolamine. Heart rate (HR) and blood pressure (BP) were recorded by a Finapres® cuff applied to the right index finger.
Results: Significant increased diastolic and systolic BP accompanied by significant decreased HR suggested the occurrence of autonomic dysreflexia (AD) during pudendal nerve stimulation. These cardiovascular changes corresponded with the subjective sensation of AD symptoms in patients of group A. Intravenous phentolamine lowered the resting BP and prevented severe hypertension during stimulation. Patients in group B presented with mild HR and BP changes in response to pudendal nerve stimulation and reported no AD symptoms.
Conclusion: Our results show a considerable effect of electrical pudendal nerve stimulation on HR and BP in patients with high SCI. This may indicate that sacral somatic afferent fibers of the pudendal nerve are involved in the neuronal mechanism of AD in SCI patients with high neurological level. Intravenous phentolamine enables pudendal nerve stimulation without the risk of severe hypertension.
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Keywords: spinal cord injury; sympathetic nervous system; autonomic dysreflexia; electric stimulation; phentolamine

Introduction

Sexual intercourse, electroejaculation and vaginal dilatation may elicit symptoms of autonomic dysreflexia (AD) in patients with spinal cord injury (SCI) on high neurological level.[1–4] These clinical and experimental observations suggest that pudendal afferent fibers might be involved in dysregulations of the autonomic nervous system after SCI. However, the underlying neuronal mechanism and involved pathways for these observations are not clear. Also, bladder and bowel distension, urinary tract infection, skeletal fractures, pain, and a variety of iatrogenic causes such as cystoscopy and electrical stimulation are known as triggering factors for AD. On the other hand, pudendal nerve stimulation is known to have a potential inhibitory effect on detrusor hyperreflexia due to SCI. The effectiveness as a neuromodulative treatment for neurogenic incontinence has been established in the last decades.[5–7] In SCI patients with high lesion levels, the occurrence of AD needs to be considered during stimulation.

In this prospective study, we assessed the effects of pudendal nerve stimulation on the cardiovascular system in a population of SCI patients in order to learn more about the underlying neuronal mechanism of AD and to estimate the potential risk during diagnostical or therapeutical pudendal nerve stimulation.

Patients and methods

The local ethical committee approved the experimental procedure. A total of 22 male patients with a complete SCI gave their fully informed consent and were included in the study.

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At the time of examination, all patients had passed the period of spinal shock (mean lesion age: 98 months, ranging from 41 to 178 months). Patients with evidence of peripheral neuropathy (diabetes mellitus, alcoholism) or peripheral nerve damage were excluded. No subject received any medication known to affect the cardiovascular system.

Patients underwent detailed neurological examination according to the ASIA protocol to define the segmental level of SCI.[8] Patients with incomplete lesions defined as any sensory or motor function preserved in the lowest sacral segment were excluded. Absent somatosensory-evoked potentials evoked by pudendal and tibial nerve stimulation confirmed complete lesions of the ascending somatosensory pathways of both these nerves. To assess conus medullaris and cauda equina function, electrophysiological recordings of bulbocavernosus and anal reflexes, as well as electromyogram and nerve conduction studies of the lower limbs, were performed and showed unaffected sacral segments in all patients.

The patients were divided into two groups according to the level of lesion: group A (C6–T6, $n=15$) and group B (T7–L2, $n=7$). Electrical impulses were generated by a Dantec Keypoint® stimulator. Biphasic rectangular impulses (0.2 ms, 10 Hz) with intensities up to 100 mA were applied to the dorsal penile nerve using disposable surface electrodes. Heart rate (HR) and blood pressure (BP) were recorded continuously by a Finapres® cuff applied to the right index finger (sampling rate 1000 Hz). Bladder pressure to identify detrusor contractions and external urethral sphincter pressure to observe the effect of stimulation were recorded by a transurethral microtip transducer (sampling rate 1000 Hz). Measurement and signal analysis was performed using Soleasy™-software package. Statistical data evaluation was done by analysis of variance for repeated measurements (level of significance: $P<0.05$).

During stimulation, the appearance of clinical AD symptoms like headache, sweating and paraesthesia were recorded from the patients. A total of 66 stimulations of the pudendal nerve for 20 s each were performed. Five patients received 7 mg of the rapid-acting alpha-blocking agent phentolamine intravenously. Pudendal nerve stimulation was repeated in these five patients, three times within the time frame of the first 20 min after injection and then once at 30 min after injection.

Results

Electrical stimulation was well tolerated in all cases. No patient reported any direct sensation from the external genitalia associated with stimulation. Patients with lesions above T6 (group A) reported mild or moderate symptoms of AD for the time of stimulation (mostly headache and sweating above the level of lesion). Patients with lesions below T6 did not note any of these symptoms during stimulation.

Patients from group A (C6–T6) presented with hypertension and bradycardia during stimulation (Figure 1). In patients with lower thoracic or lumbar lesions, HR and BP remained almost unchanged during stimulation (Figure 2). Mean initial HR decreased during stimulation in group A from 67 to 58 bpm ($P=0.0002$) and not significantly in group B from 68 to 64 bpm. Mean initial systolic BP increased during stimulation in group A from 128 to 161 mmHg ($P<0.0001$) and in group B not significantly from 126 to 138 mmHg. Mean diastolic BP increased in group A from 61 to 76 mmHg ($P=0.0003$) and in group B not significantly from 65 to 70 mmHg (Figures 3 and 4).

The intravenous application of 7 mg phentolamine in five patients from group A was well tolerated in all cases. In two patients, mild orthostatic symptoms occurred temporarily. Phentolamine lowered the resting diastolic and systolic BP and raised the resting HR.

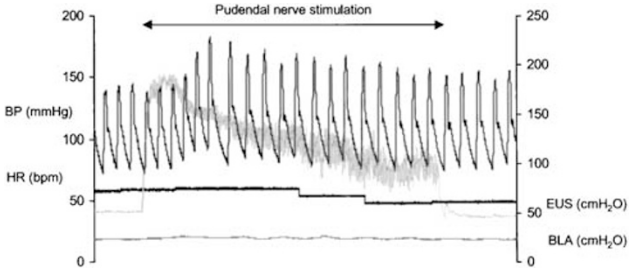

Figure 1 HR, BP, bladder pressure (BLA) and external urethral sphincter pressure (EUS) in response to pudendal nerve stimulation in a patient with complete SCI on level C6.

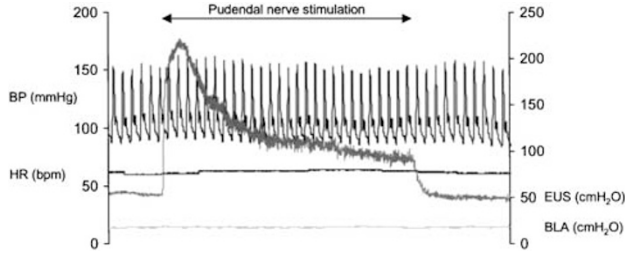

Figure 2 HR, BP, bladder pressure (BLA) and external urethral sphincter pressure in response to pudendal nerve stimulation in a patient with complete SCI on level T9.

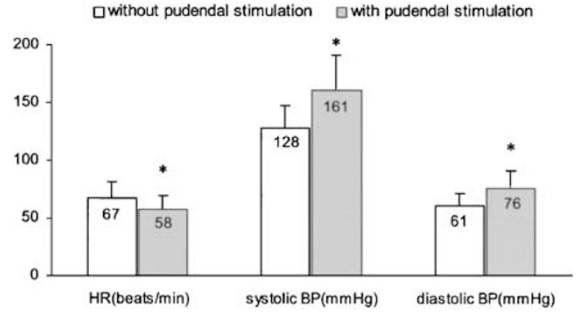

Figure 3 Mean HR and BP in response to pudendal nerve stimulation in group A (C6–T6, $n=15$, $^{*}P<0.001$ without versus with pudendal stimulation).

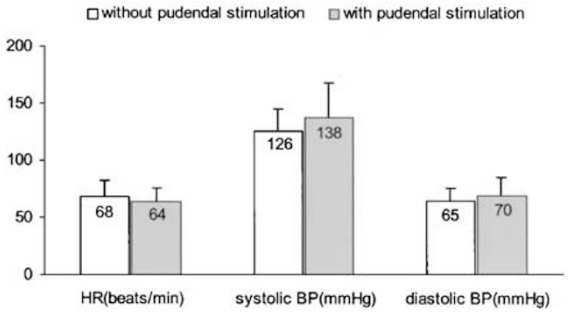

Figure 4 Mean HR and BP in response to pudendal nerve stimulation in group B (T7–L2, $n=7$).

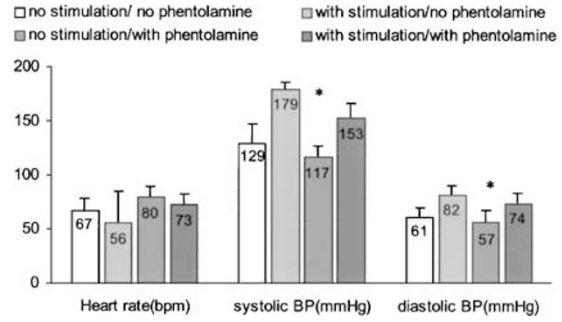

Figure 5 Mean HR and BP in response to pudendal nerve stimulation with and without i.v. phentolamine in five patients from group A ($^{*}P<0.05$, less increase in systolic and diastolic BP during stimulation with phentolamine versus the increase during stimulation without phentolamine).

During stimulation, mean initial HR decreased without phentolamine from 67 to 56 bpm and with phentolamine from 80 to 73 bpm. Mean initial systolic BP increased during stimulation without phentolamine from 129 to 179 mmHg and with phentolamine from 117 to 153 mmHg. Mean diastolic BP increased during stimulation without phentolamine from 61 to 82 mmHg and with phentolamine from 57 to 74 mmHg (Figure 5). After the administration of phentolamine, there was a significant less increase in systolic and diastolic BP during stimulation, when compared to the systolic and diastolic BP increase during stimulation without phentolamine ($P<0.05$).

Discussion

Our results demonstrate a significant cardiovascular effect of electrical pudendal nerve stimulation in SCI patients with lesions at T6 and higher. Cardiovascular dysregulation in SCI patients with severe hypertension accompanied by bradycardia and clinical symptoms like headache, anxiety and sweating suggests the occurrence of AD.[9] This symptom complex, first described in 1947,[10] usually affects only patients with lesions above the fifth or sixth thoracic level due to a lack of supraspinal control of the splanchnic sympathetic outflow at T5 and T6.[11] The disturbance of the sympathetic nervous system below the level of SCI is further complicated by a reduced overall sympathetic activity, by changes on the level of the preganglionic sympathetic neurons and by peripheral alpha-adrenoceptor hyperresponsiveness.[12,13] However, it has been recently shown that even though there is a reduced sympathetic activity the sympathetic nervous system has the capacity of huge increase in noradrenaline spillover below the level of lesion.[14] Rossier *et al*[15] first described a close relation between sexual activity, symptoms of autonomic dysreflexia and catecholamine levels in blood and urine of patients with high SCI. AD frequently occurs to distensions of hollow organs such as bladder or bowel. However, a variety of other triggering factors such as urinary tract infection, transurethral catheterization, detrusor–sphincter dyssynergia,[16] cystoscopy[17] and bladder percussion[18] have also been observed.

In a Swedish population, seven out of 48 chronic SCI patients reported on AD in response to sexual activity including ejaculation, vibrator stimulation or sexual intercourse.[19] Pudendal afferent stimulation during electroejaculation,[1–3] sexual intercourse and vaginal manipulation[4] is known as triggering factor for AD. During electroejaculation, sexual intercourse and vaginal manipulation, the pudendal afferent fibers are stimulated via the dorsal penile/clitoral or vaginal branch and seem to be directly involved in triggering AD. However, also transurethral catheterization, cystoscopy and dyssynergic sphincter contractions recruit pudendal afferent fibers from the urethra and the external sphincter. We think that these fibers might also be involved in triggering autonomic dysregulation described in literature. In a recent study, an anesthetic block of the dorsal penile nerve inhibits vibratory-induced ejaculation as well as concomitant AD in spinal men.[20] Obviously, intact penile afferents are required for both ejaculation and concomitant AD. We think, the underlying neuronal mechanism of AD in these cases involve pudendal afferent fibers that interact with spinal sympathetic neurons, controlling the splanchnic sympathetic outflow. These neurons with lost supraspinal control cause vasoconstriction and severe hypertension.

Functional electrical stimulation (FES) of skeletal muscles for movement can evoke symptoms of AD in SCI patients.[21–23] A possible mechanism for the FES-induced AD has been postulated. The electrical stimulation is perceived as a noxious stimulus by pain receptors. This nociceptive input travels via C pain fibers to the spinal cord and due to massive sympathetic discharge below the lesion resulting in vasoconstriction and hypertension.[21] However, topical skin anesthesia at the stimulation site did not influence the AD symptoms. This indicates that also other mechanisms than skin nociception are responsible for FES-induced AD.[23] Electrical pudendal nerve stimulation has been tried as a neuromodulative treatment for neurogenic bladder dysfunction. Hyperreflexive detrusor contractions were suppressed effectively.[5–7] As our results show, AD needs to be considered during pudendal nerve stimulation in patients with lesions above T6. Therefore, BP and HR

monitoring is required during pudendal nerve stimulation. Treatment options for AD are well established: removal of the triggering factor and if required symptomatic therapy using alpha-receptor blocker[24,25] or calcium-channel blocker.[26] In the present study, the intravenous application of the alpha-blocking agent phentolamine lowered the resting BP and increased the resting HR. During stimulation, the maximum BP increase was significantly reduced and severe hypertension prevented. This may suggest that phentolamine administration enables pudendal nerve stimulation without the risk of severe hypertension. The effectiveness of alpha-blocking agents seems to base on the peripheral alpha-adrenoceptor hyper-responsiveness seen in SCI patients with high lesion levels.

The involved receptors, pathways and neuronal mechanism of AD induced by pudendal nerve stimulation need to be further elaborated in order to estimate the potential risk and to prevent serious complications.

Conclusion

Pudendal nerve stimulation induces AD in SCI patients with lesions above T6. Severe hypertension should be taken into consideration during diagnostical or therapeutical stimulation of pudendal afferent fibers. The alpha-blocking agent phentolamine enables a significant reduction of BP during stimulation and may be a protective factor for SCI patients undergoing pudendal nerve stimulation.

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