Research Paper

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Autonomic dysreflexia in tetraplegic patients: evidence for α-adrenoceptor hyper-responsiveness

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A controlled study of acute pharmacological intervention was designed to determine whether decreased sympathetic nerve activity in tetraplegic patients results in increased responsiveness of α-adrenoceptors which might contribute to vascular hyper-reactivity and the clinical scenario of autonomic dysreflexia. The study took place in a university teaching hospital and included six male tetraplegic patients and six age-matched normal male controls. All tetraplegics were 5 months or longer post-traumatic spinal cord injury and all had experienced symptoms of autonomic dysreflexia on at least one occasion. The dorsal foot vein diameter was recorded with a tonometer during local infusions of noradrenaline 0.125–256 ng/min given through a short intravenous needle. In tetraplegic patients, there was a significant shift to the left of the dose–response curve indicating increased venous responsiveness to noradrenaline. The concentration of noradrenaline required to cause a 50% reduction of the resting vein diameter was decreased in tetraplegics (1.6 ng/min, geometric mean) compared to normal controls (10.9 ng/min, $p < 0.02$). α-Adrenoceptor responsiveness in dorsal foot veins is increased in patients with tetraplegia. Hypersensitivity of vascular α-adrenoceptors may contribute to autonomic dysreflexia in patients with high spinal cord injury.

Keywords: α-adrenoceptor; autonomic dysreflexia; noradrenaline; tetraplegia

Introduction

It is well established that spinal cord injury causes a major derangement in the autonomic control of blood pressure.[1] At rest, patients with tetraplegia have a lower blood pressure but heart rate remains within the normal range.[1] Resting levels of plasma noradrenaline and adrenaline are significantly lower in tetraplegics compared with normal controls.[2] This is consistent with results of direct nerve recordings from the peroneal skin nerve fascicle, showing decreased spontaneous sympathetic activity in tetraplegic patients.[3] Despite such evidence of reduced sympathetic outflow, patients may experience periodic symptoms suggestive of overactive sympathetic responses.

Autonomic dysreflexia is a clinical syndrome occurring in 90% of patients with tetraplegia or high level paraplegia where the spinal cord lesion lies above thoracic level 6 (T6).[4–6] Classic symptoms of autonomic dysreflexia include paroxysmal hypertension, bradycardia, anxiety, headache and dyspnea. Flushing of the face and neck occurs with sweating in areas above and around the level of the lesion whereas, below the level of the lesion, cold limbs and piloerection may reflect sympathetic hyperactivity.[5] The onset of autonomic dysreflexia can be readily induced by physiological stimuli such as a full urinary bladder, cold temperature or activation of skeletal muscle.[1]

As peripheral α-adrenoceptors are under constant modulation of the sympathetic nerve activity and to reconcile the above observations, we hypothesized that decreased sympathetic tone below the level of a high spinal cord injury results in hyper-responsiveness of vascular α-adrenoceptors to noradrenaline. To test this hypothesis, we studied the responsiveness of the α-adrenoceptor to local infusions of graded doses of noradrenaline in the dorsal superficial foot vein of tetraplegic patients with a history of autonomic dysreflexia.

Methods

This study was reviewed and approved by the University Review Board for Health Sciences research involving human subjects and all subjects gave written informed consent.

Six tetraplegic patients (all males, 29 ± 2.5 years; mean ± SEM) with autonomic dysreflexia were identified from the in-patient and out-patient services of a specialized referral hospital. All patients had experienced autonomic dysreflexia on at least one occasion with one or more of the following clinical signs and symptoms: sudden severe headache, increase of blood pressure, facial and cervical flushing, piloerection, sweating, dyspnea and peripheral vasoconstriction. The diagnosis was confirmed by a physician specialized in the treatment of patients with spinal cord injury. The time from the onset of spinal cord injury to study was 3.8 ± 1.9 years. The injury level of the patients studied was between C4 and C7. Four patients had complete injury (Frankel A), one patient had complete motor injury with sparing of the posterior columns (Frankel B) and one patient was 'motor useless' (Frankel C).[7] Patients who had spinal cord

injury for less than 5 months, current α-blocker treatment, or with associated cerebral trauma or infarction were excluded. Patients were compared with six normal controls (males, mean age 31 ± 3.2 years) who had no history of spinal cord injury, autonomic dysreflexia or vascular disease and who were on no vasoactive medications. Controls were identified during the same period as the study patients and participated with the knowledge that they would derive no direct benefit from the study.

All vasoactive medications were withheld for 24 h to avoid any acute hemodynamic effects over the course of the study. Patients on α-adrenoceptor antagonists were excluded from the study. To reduce edema in the foot, patients were advised to wear elastic stockings and keep the foot elevated overnight. The patients were allowed to have a light breakfast with soft drinks free of alcohol and caffeine. The bladder was emptied immediately before the study and, in patients with an in-dwelling catheter, it was allowed to drain freely during the study. All the experiments were performed in the morning. Subjects were supine and rested quietly with leg and foot comfortably supported above heart level in a temperature-controlled vascular laboratory (22–24°C). Tetraplegic patients had normal foot colour on visual inspection. A short (1.9 cm) 25-gauge needle (Butterfly-Abbocath, Butterfly-Abbot Ireland Ltd, Sligo, Ireland) was inserted into the largest dorsal superficial foot vein with a long straight section and no visible tributaries. Normal saline (0.9%) was infused at 0.4 ml/min. A lightweight electromechanical tonometer, linear variable differential transformer consisting of primary and secondary coils with a lightweight movable ferromagnetic core,[8,9] was placed vertically over the summit of that vein, 10 mm proximal to the tip of the needle. This technique is sensitive and reproducible and has been extensively reviewed recently.[10] The output signal from the tonometer was amplified and tracings were recorded on paper (LKB recorder, model 2210, LKB, Sweden). Foot vein distension was measured as the difference between the lowest baseline during the study and the height of the vein distension where it reached a plateau during proximal limb cuff inflation (45 mmHg for 2 min). When the study was completed, the tonometer was removed from the foot and calibrated in millimetres on a micrometer gauge.

The subject was left undisturbed for 30 min before 5 ml of blood was taken into a prechilled tube and the plasma separated in a cold centrifuge (+4°C). The plasma was stored at –70°C until analysis of plasma catecholamines by high performance liquid chromatography.[11] At least two recordings of foot vein distension during saline infusion were then obtained to ensure a stable baseline and the mean was taken as the control distension. Graded cumulative local infusions (0.4 ml/min) of noradrenaline diluted in saline (0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256 ng/min) were given for 5 min at each dose. In the third minute of each 5-min interval the venous occlusion cuff was inflated for 2 min to allow repeat measurement of vein diameter. Measurements were repeated in an identical fashion in all patients and normal subjects. Arterial pressure and heart rate were obtained by a semi-automated oscillometric blood pressure recorder (Dinamap 845XT, Critikon Inc., Tampa, FL, USA) in the upper arm. The experiment was terminated if systolic or diastolic pressure rose above 180 or 90 mmHg, respectively, or if the infusion of noradrenaline caused >80% venoconstriction.

Venous distension for each infusion was expressed as a percentage of the control distension. Dose–response curves (semi-logarithmic) were constructed for each subject using a non-linear curve fitting program (GraphPad InPlot version 4.0, H.J. Motulsky, San Diego, CA, USA). The concentration of noradrenaline required to cause 50% constriction (ED_{50}) of the control foot vein distension was computed and the geometric mean calculated from the log transformed data. Other values are expressed as arithmetic mean ± standard error (SE). Comparisons between groups were performed with unpaired Student's t test. Changes in foot vein distension, arterial pressure and heart rate were analyzed by analysis of variance with repeated measurements.[12] A two-tailed p value less than 0.05 was considered as statistically significant.

Results

Resting mean arterial pressure and heart rate were 77.4 ± 1.9 mmHg and 60.8 ± 4.6 beats/min in tetraplegic patients and 79.9 ± 2.5 mmHg and 58.8 beats/min in normal subjects respectively (p = NS). Plasma noradrenaline and adrenaline levels were 259 ± 58 and 18.6 ± 1.1 pg/ml in tetraplegic patients and 218 ± 33 and 20.8 ± 2.1 pg/ml, respectively, in normal subjects (p = NS). The control diameter of the foot vein at a distending pressure of 45 mmHg was the same in tetraplegic patients as in normal subjects (0.80 ± 0.13 versus 0.81 ± 0.12 mm, p = NS).

The mean dose–response curves for vasoconstriction to noradrenaline in tetraplegic patients and normal subjects are shown in Figure 1. The dose–response curve in tetraplegic patients was shifted significantly to the left. The noradrenaline ED_{50} was markedly decreased in tetraplegic patients (1.6 ng/min) compared to age- and sex-matched normal controls (10.9 ng/min, $p < 0.02$). There was a trend towards an increase in mean arterial pressure during the infusions of noradrenaline in tetraplegic patients but the difference did not reach statistical significance compared with normal controls (Figure 2). Heart rate remained stable during the study in both groups. In one tetraplegic patient, the experiment was stopped because the arterial pressure increased to 152/95 mmHg during infusion of noradrenaline at 8 ng/min.

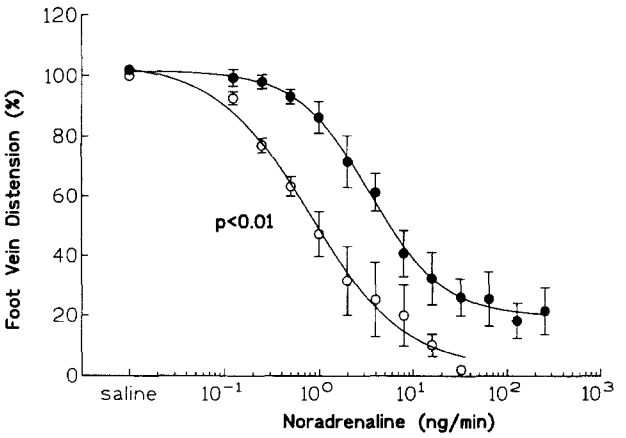

Figure 1. Semi-logarithmic dose–response curves of dorsal foot vein distension at 45 mmHg, expressed as a percentage of distension during baseline 0.9% saline infusion, during local sequential graded infusions of noradrenaline in tetraplegic patients and age-matched normal subjects. ○, Tetraplegics (n = 6); ●, normal subjects (n = 6)

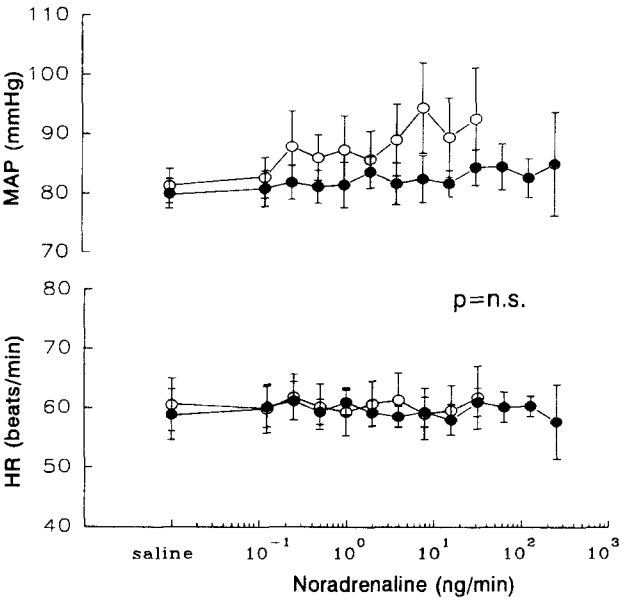

Figure 2. Changes in systemic mean arterial pressure (MAP) and heart rate (HR) during local venous infusions of noradrenaline in tetraplegic patients and age-matched normal subjects. ○, Tetraplegics (n = 6); ●, normal subjects (n = 6)

Discussion

The present study clearly demonstrates increased responsiveness of venous α-adrenoceptors to locally infused noradrenaline in the foot vein of tetraplegic patients with a history of autonomic dysreflexia. The results were similar in all patients and were in marked contrast to those obtained in age-similar normal subjects who required a six- to sevenfold increase in noradrenaline concentration to produce a comparable 50% venoconstriction. Although not specifically addressed in this study design, the results are consistent with the hypothesis that hypersensitivity of vascular α-adrenoceptors may be important in the manifestation of autonomic dysreflexia in patients with tetraplegia.

In a previous study, Mathias *et al.*[13] showed that the systemic pressor response to intravenous noradrenaline infusion was enhanced in tetraplegic patients. However, the arterial pressure response to intravenous noradrenaline is influenced by the functional status not only of the vasculature, but also of the heart and the baroreceptors. Sympathetic denervation of the heart with high level spinal cord injury may lead to adrenoceptor up-regulation in the myocardium mediating in part an enhanced pressor response to noradrenaline. Although the significant vascular response in tetraplegic patients was accompanied by a bradycardia, for the same increase in arterial pressure the decrease in heart rate was less in tetraplegic patients than in normal subjects,[13] indicating a reduced baroreflex response which would also exaggerate the true pressor responsiveness to noradrenaline in these patients.

The advantage of the current study design is that full dose–response curves to noradrenaline could be constructed in the dorsal foot veins with negligible or very low systemic doses of noradrenaline. Thus vascular α-adrenoceptor responses could be more easily and accurately isolated. In normal control subjects, the arterial pressure was stable during the whole period of noradrenaline infusion. However, slight but non-significant increases in systemic arterial pressure were observed during the infusions of noradrenaline in tetraplegic patients and in one patient diastolic pressure rose above 90 mmHg. These observations suggest that the hypersensitivity of α-adrenoceptors which we directly observed in veins may also be present in arteries and this would be important in understanding the pathophysiology of autonomic dysreflexia in these patients.

Autonomic dysreflexia can occur with visceral or cutaneous stimuli, often noxious, which originate from below the level of the spinal cord lesion and most commonly arise from the bladder or less often as a consequence of bowel impaction or a pressure sore. The afferent nerve impulses from these stimuli enter the spinal cord and may ascend in the dorsal and spinothalamic tract; as they ascend, collateral connections are thought to activate the intermediolateral column of the spinal cord up to the level of the spinal cord injury and lead to sympathetic efferent outflow activity.[14] This sympathetic outflow may be increased due to the lack of supraspinal inhibition in tetraplegic patients resulting in symptoms of autonomic dysreflexia. The present results support the hypothesis that the marked blood pressure response seen in autonomic dysreflexia in tetraplegic patients is mainly due to increased vascular α-adrenoceptor responsiveness. This hypothesis is further supported by evidence from Krum *et al.*[15] that, although bladder distension significantly increases arterial pressure in tetraplegic patients compared with normal subjects, there were no significant changes in plasma noradrenaline levels in these patients to account for the blood pressure rise and they concluded, therefore, that the rise in pressure may be consistent with increased vascular sensitivity.

In high spinal cord injured patients, the sympathetic denervation is essentially pre-ganglionic.[13] Loss of preganglionic facilitatory influences would result in

diminished postganglionic sympathetic activity and this has been confirmed directly with recordings of peroneal nerve sympathetic activity.[3] Recent studies show that, although noradrenaline spillover rate is reduced in tetraplegic patients, noradrenaline clearance is the same as in normal control subjects.[16] Therefore, the increased local venous response to infused noradrenaline observed in the present study is not due to reduced clearance of noradrenaline but is related to increased vascular α-adrenoceptor responsiveness. Locally infused noradrenaline may also stimulate extrajunctional α_2-adrenoceptors which mediate constriction and $ß_2$-adrenoceptors which mediate dilation, but the principal effect is on α_1-adrenoceptors which are the predominant subtype[17,18] and are located postjunctionally within the synapse and therefore also reflect response to neuronally released noradrenaline.

Only six patients were required to show a significant and marked increase in α-adrenoceptor responsiveness. However, this relatively small number may have been insufficient to demonstrate and confirm reduced circulating levels of catecholamines reflective of a generalized reduction in sympathetic efferent traffic. Furthermore, the similar venous catecholamine levels and resting blood pressures between the two subject groups may reflect the carefully controlled conditions of the experiment in a quiet, temperature-controlled room, with all measurements being performed in the supine position after a 30 min rest and equilibration period.

In conclusion, venous α-adrenoceptor responsiveness to noradrenaline is significantly increased in tetraplegic patients with autonomic dysreflexia compared to normal subjects. This hypersensitivity of vascular α-adrenoceptors may contribute to the manifestation of autonomic dysreflexia in patients with high spinal cord injury. Further studies would be required to determine which receptor subtypes are most markedly affected, whether the increased α-adrenoceptor responsiveness is due to increased receptor density or enhanced post-receptor mechanisms, whether changes in venous and arterial adrenoceptor responses occur with equal magnitude and if the time-course of changes in adrenoceptor function parallel the development of autonomic dysreflexia.

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