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CUTANEOUS VASOMOTOR SENSITIVITY TO NORADRENALIN IN SPINAL AND INTACT MAN

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ABSTRACT. It has been suggested that the increased pressor response to noradrenalin found in tetraplegic patients is due to absence of blood pressure restraining reflexes. However, it has also been found that below the lesion in such patients cutaneous vessels, which in intact man are not under baroreflex control, show prolonged vasoconstriction after sympathetic neural discharges. This finding might indicate that cutaneous blood vessels display an increased sensitivity to noradrenalin in spinal patients. To investigate this, photoelectric cutaneous pulse plethysmograms were monitored during i.v. noradrenalin infusions in six patients with spinal cord injuries and in six intact subjects. There were no significant differences between the groups in either extent or duration of vasoconstriction. The findings provide no evidence that increased sensitivity to noradrenalin is a factor of importance for the attacks of hypertension in tetraplegic patients.

Key words: Spinal man, autonomic dysreflexia, noradrenalin, supersensitivity

Autonomic dysreflexia, comprehensively described by Guttmann & Whitteridge (7), constitutes a major problem in many patients with spinal cord lesions at cervical and upper thoracic levels. Indirect methods (using sympathetic effector responses and neuro-hormone levels as markers of nerve activity) (6) have suggested that sympathetic mechanisms are involved in this phenomenon. The use of the term "sympathetic hyperreflexia" reflects the view that these autonomic reactions could be due to inhibited sympathetic activity. On the contrary, direct microneurographic recordings of sympathetic activity in peripheral nerves below the level of the lesion in spinal patients recently have shown (11, 12) that spontaneous sympathetic activity is very sparse and that stronger stimuli were needed to induce sympathetic reflex discharges in spinal than in intact man. Furthermore, nerve recordings during bladder expansion showed pronounced cutaneous vasoconstriction and hypertensive reactions but only moderate increases in sympathetic activity, never reaching the level found in many intact subjects at rest. Thus, sympathetic activity in spinal man seems to be decreased rather than increased. One cause for the hypertensive reactions would be lack of blood pressure controlling reflexes which might explain the increased blood pressure responses to infused noradrenalin (the main transmitter of sympathetic nerve endings (4)) found in tetraplegic patients (10). Wallin (12), however, showed that following a single sympathetic nerve burst cutaneous vasoconstriction was of significantly longer duration below the level of the lesion in spinal patients compared to findings in intact subjects. Since cutaneous vessels are not under appreciable baroreflex control (1), this finding is not likely to be due to lack of blood pressure restraining reflexes, but might be explained by supersensitivity to noradrenalin. If so, it may be of importance for the hypertensive reactions in spinal patients.

The aim of this investigation was to test whether sensitivity to noradrenalin in vessels normally without baroreflex control, i.e. skin vessels, was increased in patients with spinal cord injuries.

METHODS

Material

Experiments were made on six intact male subjects aged 25–31 years and on six patients 2–21 years after traumatic spinal cord injuries with their informed consent. The study was approved by the Ethical Committee of the Medical Faculty of the University of Uppsala. Some basal patient data are presented in Table I. Two patients had patches of weak preserved sensibility, but none had voluntary motor function below the level of the lesion. Cortical sensory potentials (SEP) could be evoked from electrical stimulations of peroneal and tibial nerves in one of the patients. Thus, in two patients (nos. 5 and 6) the lesions were not functionally complete, whereas the others showed no sign of incompleteness. Two tests, however, indicated completeness from sympathetic standpoint in all patients: (*a*) Plethysmographic responses on hand or foot (for paraplegic patients on foot) could be induced only by stimuli applied distal but not proximal to the level of the lesion. (*b*) Direct recordings of sympathetic activity in the peroneal nerve showed sym-

Table I. *Patient data*

Patient no. and sex	Patients age (yrs) at date of first experiment	Age of lesion (yrs) at date of first experiment	Level of lesion	Completeness of lesion	Relevant medication
1 M	39	21	C6	Clinical: Complete SEP: Not performed	0
2 F	38	10	C5	Clinical: Patches of sensibility on big toes SEP: No response	Baclofenum 200 mg
3 M	28	10	C6	Clinical: Complete SEP: No response	Baclofenum 50 mg
4 M	16	2	C6	Clinical: Complete SEP: No response	0
5 M	21	3.5	T7	Clinical: Small area of very weak sensibility at left knee SEP: Responses from both legs	0
6 M	27	3	C6	Clinical: Complete SEP: No response	0

pathetic activity with characteristics different from what is found in intact subjects, but consistent with the sympathetic activity found in nerves deprived of supraspinal influence in other patients (11, 12). Two patients were on medication (baclofenum). None of the intact subjects were so.

Experimental procedure

Two experiments were made on each subject. 1) In one session cutaneous vasomotor respones to single sympathetic nerve bursts, visualized by microneurography, were studied. 2) In the other session cutaneous vasomotor responses and blood pressure following noradrenalin infusion were studied. The two experiments were made within an interval of maximum 15 months.

1. Microneurographical recordings were made via insulated tungsten electrodes with uninsulated tips of a few μm inserted into the peroneal nerve at the fibular head. The nerve was localized by electrical stimulation through the electrode. When a nerve fascicle had been impaled it was identified as a muscle fascicle or skin fascicle according to (*a*) the response to electrical stimuli (muscle twitching or, in intact subjects, skin paraesthesiae, respectively) and (*b*) the type of stimulus (muscle stretching or light skin touch) giving rise to mechanoreceptor afferent activity. Minor adjustments of the electrode were made until a site was found in which sympathetic activity (5, 8, 11, 12) was encountered. In intact subjects recordings were made from skin nerve fascicles. In spinal patients recordings were made from either fascicles to skin or muscle, since sympathetic outflow to skin and muscle below the level of the lesion in spinal patients are similar (11). For detailed descriptions of the microneurographical technique and for the criteria for sympathetic activity in intact and spinal man see Hagbarth (8), Wallin (12) and Stjernberg (11). In intact subjects sympathetic reflex discharges were elicited by electrical skin stimulations and in the patients by electrical skin stimulations, skin pinches or pressure over the urinary bladder. Changes of volume of cutaneous vessels were monitored by photoelectric pulse plethysmographs (van Gogh ILP-ZA) on the plantar side of the ipsilateral big toe. In two intact subjects recordings were made both at normal room temperature and while they were heated in a box, ordinarily used for hypo-thermic surgery (Auto Hypo Therm, Super Automatic Neurosurgery XM, Heljestrand, Stockholm). The signals were stored on a tape (recorder Sangamo Sabre VI) and analyzed later as described below.

2. The subjects were supine and rested for 25 min before the infusions were commenced. Noradrenalin was diluted in isotonic saline containing ascorbic acid (20 μg/ml) and was infused into an antecubital vein in a stepwise manner, starting at 0.1 $nmol \times kg^{-1} \times min^{-1}$ (spinal patients) or 0.2 $nmol \times kg^{-1} \times min^{-1}$ (intact subjects). The infusion rate was doubled every 10 min until systolic blood pressure had increased by 40 mmHg, when the infusion was interrupted. During the noradrenalin infusions vasomotor responses to circulating noradrenalin were studied. Cutaneous vasomotor responses were recorded with pulse plethysmographs on both index fingers (two intact subjects and one tetraplegic patient) or on the plantar side of the big toe (four intact subjects and five patients). To eliminate ongoing sympathetic activity as a cause for vasoconstriction the nerve to the area from which the plethysmogram was recorded (i.e. the median or the medial plantar nerve) was unilaterally blocked with local anaesthesia (bupivacain) at the level of the wrist or ankle in both intact and spinal subjects. The nerve was located by muscle twitch responses to electrical stimuli delivered through an infusion needle (isolated except at the tip) which was also used for injecting the anaesthetic. The anaesthesia was considered complete when twitches were no longer obtained and when cutaneous vasomotor responses to electrical skin stimuli were obtained only at the non-blocked side. Blood pressure was measured with a cuff on the arm contralateral to the infu-

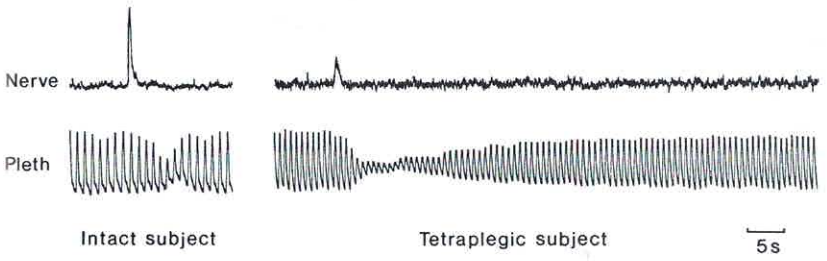

Fig. 1. Relationship between reflex sympathetic discharges in skin nerves and cutaneous vasoconstriction in an intact subject and a tetraplegic patient.

sion twice during the rest period, 4 and 9 min after each change of infusion rate, and 3, 6, 11 and 16 min after the end of infusion. The pulse plethysmogram was stored on tape and analyzed later.

The duration of the cutaneous vasomotor responses to single nerve bursts was calculated in the following way: The mean amplitude of the last ten pulses in the plethysmogram before the stimulus was determined. Vasoconstriction was considered terminated when pulse amplitudes had returned to 90% of the prestimulus amplitude. The cutaneous vasomotor responses to noradrenalin infusion were calculated from the plethysmogram in two ways: (*a*) The amplitudes of ten pulse waves in the plethysmogram were measured at rest and at the end of the different steps of infusion. (*b*) The duration of vasoconstriction after the end of infusion was calculated. Vasoconstriction was again considered terminated when pulse amplitudes had returned to 90% of the amplitude at rest.

The results were analyzed by Student's two tailed *t*-test on non-paired values and by the Mann-Whitney rank sum test.

RESULTS

The stimuli used to induce reflex sympathetic bursts were experienced as unpleasant by all the intact subjects, but, short of the bladder pressures, were not noticed at all by the spinal patients. However, the appearance of the bursts were similar and the signal-to-noice ratio equally good in the two groups. In spite of this, reduction of the amplitude in the plethysmogram with 50% or more was easily elicited by single sympathetic nerve bursts only in the spinal patients, whereas in the intact subjects vasoconstriction was very weak (only in one subject reducing pulse am-

Table II

	Duration of cutaneous vasoconstriction following sympathetic nerve burst	Cutaneous vasoconstriction (−) and vasodilatation (+) in per cent of amplitude of the plethysmogram at rest at comparable rates of noradrenaline infusion		Duration of cutaneous vasoconstriction after end of infusion
	(s)	0.2 nmol×kg×min	0.4 nmol×kg×min	(min)
Patient				
1	52	−33	−40	25.0
2	107	−27	−37	6.0
3	26	+10	−11	3.0
4	21	−49	−52	9.0
5	35	+19	+ 5	1.0
6	53	−18	−	1.5
Mean	49	−16	−27	7.6
SD	31.2	26.1	23.3	9.0
Subject				
A	13	0	+17	0[a]
B	11	− 7	−21	3.0
C	8	−12	−16	2.5
D	0	−31	−50	3.5
E	11	+ 4	+ 2	0[a]
F	0	−10	−22	2.3
Mean	7.2	− 9.3	−15	1.9
SD	5.8	12.2	22.9	1.5

[a] No vasoconstriction.

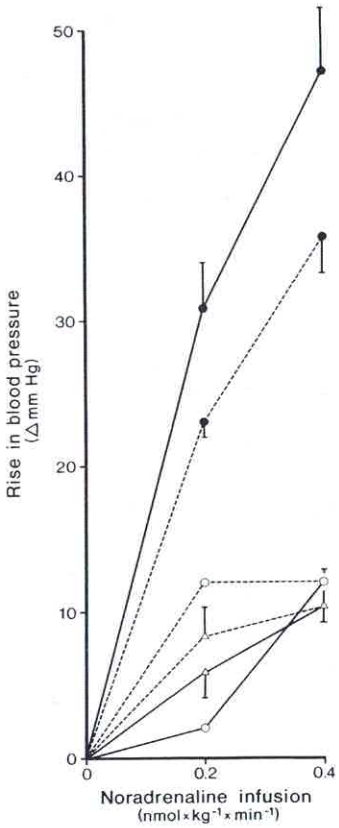

Fig. 2. Rise of blood pressure (mean and SEM) at comparable rates of noradrenalin infusion in tetraplegic (●), paraplegic (○) and intact (△) subjects. Continuous line = systolic blood pressure, dotted line = diastolic blood pressure.

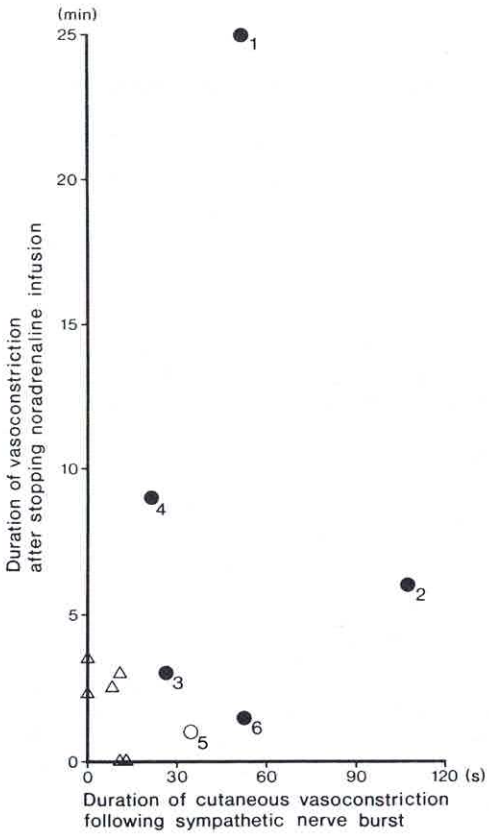

Fig. 3. Relationship between duration of vasoconstriction after stopping the noradrenalin infusions and duration of vasoconstriction following sympathetic nerve burst in tetraplegic (●), paraplegic (○) and intact (△) subjects.

plitude with more than 50% and in two subjects not at all).

The duration of plethysmographic pulse amplitude reductions following an induced sympathetic nerve discharge (summarized in Table II and exemplified in Fig. 1) was significantly longer ($p<0.01$) in spinal patients (49.0±12.7 s (mean ± SEM), range 21–107 s) than in intact subjects (7.2±2.4 s, range 0–13 s). To test whether the different cutaneous vasomotor responses to sympathetic nerve discharges in intact and spinal subjects were due to different degree of vasodilatation at rest two intact subjects were studied both at room temperature and during heating. Heating increased skin temperature from 24°C to 33°C and increased pulse amplitudes in the plethysmogram about 200% and 400% respectively but did not affect nerve discharges or duration or magnitude of vasomotor responses.

Blood pressure elevation at the end of the infusions was similar in all subjects since infusions were interrupted when systolic blood pressure had increased about 40 mmHg. At each rate of infusion, however, both the systolic and the diastolic blood pressure were higher in tetraplegic patients than in intact subjects (Fig. 2). It is worth noting that the patient with a lesion at T 7 did not rise in blood pressure more than the intact subjects.

In most intact subjects an infusion rate of 1.6 $nmol \times kg^{-1} \times min^{-1}$ was possible. Due to rise of blood pressure infusion rates more than 0.4 $nmol \times kg^{-1} \times min^{-1}$ were not possible in three tetraplegic patients. In one tetraplegic patient (no. 2) and in the paraplegic patient 0.8 $nmol \times kg^{-1} \times min^{-1}$ noradrenalin was tolerated. On the contrary, in patient 3 the infusion had to be stopped at 0.3 $nmol \times kg^{-1} \times min^{-1}$ because of complaints of head-

ache. There were no other symptoms or signs of autonomic dysreflexia during the experiments.

The pulse plethysmogram was stable during the experiments without transitory variations of the amplitude. Since in most patients infusion rates more than 0.4 $nmol \times kg^{-1} \times min^{-1}$ were not tolerated, comparisons of amplitude reductions between the groups were only made at 0.2 and 0.4 $nmol \times kg^{-1} \times min^{-1}$. The duration of vasoconstriction was measured from end of infusion, independent of the final rate of infusion. The reduction of the amplitude during infusions was slightly greater in spinal patients than in intact subjects, $-16 \pm 10.7\%$ (mean and SEM) at infusion rate 0.2 $nmol \times kg^{-1} \times min^{-1}$, and $-27 \pm 9.5\%$ at 0.4 $nmol \times kg^{-1} \times min^{-1}$ in patients, versus $-9.3 \pm 5.0\%$ and $15 \pm 9.4\%$, respectively, in intact subjects. Likewise mean duration of cutaneous vasoconstriction after the end of infusion was longer in patients (9.0 ± 3.7 s) than in normal subjects (1.9 ± 0.6 s).

The results are summarized in Table II. Variation within the patient group was considerable and especially patient 1 showed extremely long lasting vasoconstriction after end of infusion (Fig. 3). The differences between the groups, however, were not significant neither in extent nor in duration of vasomotor responses to noradrenalin by either t test or rank sum test. Furthermore, there was no significant correlation between cutaneous vasomotor responses induced by noradrenalin infusions and by nerve bursts in either of the groups as seen from Fig. 3.

DISCUSSION

Previous (10, 12) and present findings of increased pressure response to noradrenalin and of prolonged cutaneous vasoconstriction following sympathetic nerve discharges in spinal patients might be explained in various ways.

The fact that cutaneous vasoconstriction was not recorded distal to the nerve blockings when stimuli were applied proximal to the blockings indicates that neural and not humoral mechanisms were involved. Medication does not seem to be of significance for the responses since prolonged vasomotor responses were also recorded in patients without pharmacological treatment both in present and previous (12) recordings.

Due to sparse ongoing sympathetic activity (11, 12) cutaneous vessels might be more dilated at rest in the spinal patients, which could also be of importance for the prolonged vasoconstriction in these patients. The finding in two intact subjects that vasoconstriction following sympathetic nerve discharge was not increased during heat induced vasodilation speaks against such a mechanism. It is not likely that the differences in magnitude and in duration of cutaneous vasoconstriction following sympathetic nerve bursts found in intact subjects and in spinal patients were due to different sympathetic reflex activity since the signal-to-noise ratio was equally good in both groups.

Lack of baroreflex control is most certainly of importance for the attacks of hypertension in tetraplegic patients (10). However, lack of controlling reflexes cannot be the only explanation for these attacks, since sympathetic activity in tetraplegic patients is low, and even during pronounced cutaneous vasoconstriction and hypertension does not reach the level of activity found in intact subjects at rest (11). Furthermore, absent baroreflex control cannot explain the increased cutaneous vasoconstriction following sympathetic nerve discharges, since cutaneous vessels are not under baroreflex control (1).

Changes in noradrenalin metabolism could also explain the increased vasomotor reactions in spinal patients. However, this explanation does not seem likely, since Mathias (10) found no significant differences between intact subjects and tetraplegic patients in this respect either during or after noradrenalin infusions. Supersensitivity to noradrenalin due to sympathetic lesions, either at postganglionic level (3) or preganglionic level (9) would be a possible explanation both to the attacks of hypertension and to the increased reactivity of cutaneous vessels in tetraplegic patients.

The results of the present investigation, however, do not provide evidence that supersensitivity mechanisms are involved in the latter reactions. There were no significant differences between spinal patients and intact subjects either in extent or duration of cutaneous vasomotor responses to noradrenalin, although responses varied within both groups. This variation was not due to transitory variations of the amplitudes in the plethysmogram, nor, in the patients, to varying completeness of the sympathetic lesion or other clinical parameters. The reason for the very long lasting vasoconstriction in one patient is obscure. Independent of the varying vasoconstriction in the patients it is clear that patients with pronounced vasoconstriction during and after noradrenalin infusion did not always show longlasting vasoconstriction following sympathetic nerve discharges

and vice versa. This lack of correlation between the degree of cutaneous vasoconstriction induced by noradrenalin infusion and the degree of vasoconstriction induced by neurally released noradrenalin is inconsistent with a supersensitivity mechanism, since one would then expect an increased effector response to noradrenalin independent of its source.

Present results thus support the conclusion of Mathias (10) that supersensitivity to noradrenalin does not explain the increased vasomotor responses in tetraplegic patients. The regulation of cutaneous blood flow, however, is complicated and includes not only sympathetic vasoconstrictor activity (5) but also vasodilatory mechanisms (2). One possible explanation for the increased vasoconstriction following sympathetic nerve activity below the level of the lesion in spinal patients would be a disturbed balance between vasoconstriction and vasodilatator mechanisms in the absence of supraspinal control.

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