Original Article

Bedside assessment of sympathetic skin response after spinal cord injury: a brief report comparing inspiratory gasp and visual stimulus

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Study design: A case control study in five controls, and 20 tetraplegic and paraplegic patients, complete and incomplete.

Objective: The aim was to assess the feasibility of a simple test for sympathetic system preservation after spinal cord damage in a pain-free manner and which could be undertaken worldwide without specialist equipment or manpower.

Settings: Patients were attending the Southport Regional Spinal Injuries Centre, England, either as outpatients or as in-patients during rehabilitation.

Methods: The sympathetic skin response (SSR) was recorded on a single-channel ECG recorder from the right hand and right foot in turn after inspiratory gasp (IG) or visual stimulation.

Results: Unlike the visually evoked SSR, the gasp-evoked SSR was reliable, albeit of variable amplitude, and there was little difference between the hand and foot. Paraplegics had similar SSRs in the hands as the controls. There was minor insignificant habituation of response for the gasp reflex. There was occasional unexpected SSR distally in patients with complete lesions, and in patients with incomplete lesions the responses could not have been predicted from the sensory motor pattern.

Conclusions: Trained IG induces an SSR which is sufficient to elucidate sympathetic loss following spinal cord injury. It is superior to visual stimulation in this respect. Habituation is not a problem with at least 1 min between tests, and high doses of anticholinergics agents may impair the response.

Spinal Cord (2006) **44**, 217–221. doi:10.1038/sj.sc.3101821; published online 20 September 2005

Introduction

There is a need to be able to examine the state of the sympathetic system and incorporate the findings into a scoring system alongside the American Spinal Cord Association sensory motor score.[1,2] The sympathetic skin response (SSR) is the surface voltage change resulting from a stimulus associated with the cholinergic sweat glands. The skin galvanometric response (SGR) is the change in resistance to current flow associated with change in skin blood flow and both responses have been used to look for interruption anywhere along the relay between the afferent fibres, through the intermediolateral horn cells, and out through the pre- and then postganglionic efferent sympathetic fibres.

A range of stimuli can provoke these responses, both endogenous such as emotion or the inspiratory gasp (IG) reflex, and exogenous, such as peripheral nerve stimulation or a 95 dB auditory click or magnetic stimulation.[3] Generally it is observed that there is variability in amplitude response associated with the different techniques, different stimuli, stimulus interval, habituation, skin temperature, filter settings, medication and age,[4–8] which has contributed to difficulty in arriving at a consensus for a measurement technique. This being so, the ability to demonstrate any SSR response by any convenient test, repeatable without being painful, may be taken as indicative as preservation of at least some sympathetic function in the tested part.

Of six publications on techniques for eliciting SSR after spinal cord injury,[1,3,9–12] five have used electrical stimulation including of the supraorbital nerve and Carriga *et al*'s[9] group noted that it may be necessary to stimulate at five times the motor threshold, which would be painful if there were dissociation between sympa-

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thetic loss and sensory preservation. Ellaway *et al*[1] have recently investigated IG in Spinal cord injury (SCI) with good results in comparison with auditory click. In the ongoing search for a simple method the present authors wished to investigate whether a visual stimulus (VS) might be as effective as IG; so the purpose of this study was to compare the reproducibility of the IG SSR with the VS SSR, and also to assess the ability of a three-lead ECG to display this response.

Methods

Subjects

Five control subjects (mean age 37.4 ± 12.3 years) recruited in addition to 20 subjects with stable SCI (43.1 ± 14.0 years), were selected to represent a spectrum of tetraplegic and paraplegic subjects, some with complete lesions and others with incomplete lesions. They were recruited from among in-patients undergoing rehabilitation or outpatients, and exclusion criteria were diabetes mellitus and age over 70 years. The project was reviewed by the local research Ethics Committee and subjects consented in accordance with standard procedures.

Experimental procedure

At the stage of consenting, subjects were instructed to practise achieving their maximal measurable vital capacity by rapid IG. Later, subjects lay supine in a quiet examination room at an ambient temperature of $22°C$ and were connected to a 'Cambridge VS4' single-channel ECG recorder by means of a pair of surface electrodes; the anode, right limb lead, being placed on the palm or sole of the right hand or foot, and the cathode, left limb lead, being placed on the dorsal surface. The remaining leads were connected indifferently to the opposite limb. Normally the gain was set at $10 \, mm/mV$ and, with the recording paper running at $20 \, mm/s$ until a steady isoelectric trace was obtained, the patient was primed for rapid inspiration upon which the event marker was pressed simultaneously by one of the authors. The visual response was elicited by sudden presentation of a series of illustrated cards in a standard order. A minute lapsed between each successive stimulus. To test for the effect of habituation, two gasps were taken, followed by three visual stimuli, followed by two further gasps. The same sequence was repeated for the lower limb.

Analysis

The controls' averaged SSR amplitudes were compared between hand and foot, and between IG and VS by Wilcoxon's ranked sign test. Within each group, evidence of habituation was sought. Comparisons between the groups were made with the Kruskall–Wallis test. In addition, limited descriptive comparisons could be made between the neurological groups. Latencies were recorded but not analysed statistically because of a lack of electronic triggering of stimulus onset.

Results

There was no significant difference among the controls in the IG-evoked SSRs between hand and foot, but the VS SSRs were significantly less in both hand and foot ($P < 0.05$) (Table 1), and in some cases no visual responses could be obtained. The standard deviation is indicative of the amount of intra- and inter-individual variation in the voltage responses; for example, the lowest voltage in a control was 0.05 and the largest was $2.8 \, mV$. The four sequential gasp responses in the hand averaged among controls and paraplegics (15) declined somewhat from 1.1, 1.05, 0.63 to $0.70 \, mV$ for the fourth gasp but did not reach statistical significance.

The subjects' ASIA neurological impairment and anticholinergic medication is charted in Table 2 together with the presence or absence of IG SSRs in hand or foot. Unexpectedly, two complete tetraplegics (7,18) showed IG SSRs in the hand, though not the foot, and an IG SSR of $0.02 \, mV$ was obtained in the hand of one with incomplete tetraplegia. The complete paraplegia group, with the exception of case 10 with a syrinx, showed the absence of SSR in the lower limb. Three out of four with incomplete paraplegia had sympathetic loss.

There were three patients within the two paraplegic groups (4,11,14) taking oxybutynin who all gave good responses in their hands (Tables 1 and 2), and so their responses were pooled along with the other patients in their neurological cohort. Patient 14, who had been taking $10 \, mg$ daily at the time of initial testing, had a further evaluation after his requirement for oxybutynin had been increased to $20 \, mg/day$, at which dose he was aware of dryness. The mean hand gasp SSR was reduced from 0.75 to 0.26 and the waveform configuration changed from biphasic to monophasic.

The SSR latencies in controls were 1.6 (± 0.47) s (IG) and 1.69 (± 0.81) s (VS) at the hand and 1.87 (± 0.53) s (IG) at the foot, but the very low VS SSR in the feet accounted for an artefactually low latency of 4.0 s. The

Table 1 Sympathetic skin response amplitudes in controls (five) in the hand and foot after inspiratory gasp (IG) and visually evoked (VE) stimuli

Hand	Mean (mV)	Std deviation	Foot	Mean (mV)	Std deviation
IG SSR*	1.03	0.68	IG SSR*	1.2	0.67
VE SSR	0.26	0.2	VE SSR	0.03	0.07

*$P < 0.05$ for IG *versus* VE SSRs

Table 2 Subjects' clinical details

	Subject	Age (years)	Gender	Level of injury	Impairment scale (ASIA)	Oxybutynin	IG hand response	IG foot response
Group 2	1	46	m	C5	A		−	−
Age (year)	2	58	m	C5	A		+	−
44.2±10.9	7	45	m	C6	A		+	−
	12	53	m	C5	A		−	−
	15	33	m	C5	A	5 mg bd	−	−
	18	30	f	C8	A	15 mg nocte	−	−
Group 3	3	24	m	C6	B		−	−
Age (year)	6	31	m	C5	B		−	−
39.5±14.3	8	49	f	C4	C	10 mg nocte	−	−
	17	54	f	C5	D		+	−
Group 4	10	56	m	T6	A		+	+
Age (year)	13	65	m	T12	A		+	−
41±18.7	14	35	m	T8	A	10 mg nocte	+	−
	16	18	m	T7	A		+	−
	19	49	m	T6	A		+	−
	20	23	m	T8	A		+	−
Group 5	4	50	f	T8	B	5 mg tds	+	−
Age (year)	5	65	m	L2	B		+	−
48.3±13.6	9	46	m	T1	B		+	−
	11	32	m	T12	B	2.5 mg bd	+	+

ASIA impairment scale: A = complete; B = sensory incomplete, motor complete below neurological level including S4–S5; C = incomplete, motor function preserved below neurological level with more than half key muscles grade less than 3; D = incomplete, at least half key muscles below neurological level grade 3 or greater

latencies at the hand in the two paraplegic groups combined appeared to be shorter compared to the controls: 0.93±0.63 s (IG SSR) and 0.84±0.54 s (VS SSR).

Discussion

The importance of knowing the state of preservation of the sympathetic nervous system resides in charting recovery, assessment of postural hypotension, prediction of autonomic hyper-reflexia and dependent oedema and vulnerability of the neuropathic skin.[13] The neurological assessment and scoring is incomplete without this, but most techniques described have required one or other type of dedicated apparatus with operator skills that will not be universally available, and could cause the patient electrical discomfort or involve loud auditory clicks (95 dB). The hope that the noninvasive visually evoked (VE) SSR might prove reliable was not fulfilled in this study.

Technique critique
A consistent finding of all researchers has been the variability in SSR response whatever the technique. For example, Chu and Chu[7] described four types of SSR responses in able-bodied subjects following magnetic stimulation or electrical stimulation of the median nerve, and they considered only 25% normal. Drory and Korczyn[8] noted that the electrically induced response was absent in a significant proportion of older subjects. Intrinsic amplitude variability was also found in magnetically evoked SSRs amounting to 1.40±1.38 mV in the hands of paraplegic patients.[3]

There have been 12 publications looking specifically at changes in the sympathetic tone induced by IG, two of which found some variability that could be related to breathing pattern and phase of cycle.[14,15] In a study on healthy volunteers[16] the IG and expiratory gasp responses were similar and remained consistent whereas those induced by electrical stimulation were of lower amplitude, showed variable waveforms and demonstrated fade. Ellaway et al[1] provoked the SSR by either an auditory click or IG (as well as bladder tap as an infra-lesional stimulus). In four out of 21, the IG did produce an SSR, which had been negative after auditory click. These authors had noted in an earlier paper using infra-lesional electrical stimulation[9] that in cases with a negative response to electrical stimulus, it had been necessary to increase the intensity to five times the motor threshold which would have been painful if the pain sensation had been preserved in the area of stimulation to elicit the SSR.

In contrast, in the study by Hay et al[6] the IG could not be elicited in two out of 58 volunteers, the only study to have found this. The authors did not state how they

had trained the volunteers to achieve the maximum inspiratory effort. Rapid inspiration[4,17] and expiration[16] both induce an SSR, but since tetraplegic persons are unable to expire rapidly it would be best to instruct the tetraplegic subjects prior to testing using an incentive spirometre, targetting maximum inspiration within 1 s since it is the rate of change, or effort, which seems to be the important factor.[18] The 60 s allowed between responses in Hay's[6] study, as well as the present study, is below the recovery time recommended by Mueck-Weyamnn and Rauh,[5] who recommended at least 90 s rest. These authors also noted the great variability in amplitude responses induced by auditory stimuli, in which the standard deviation was not far short of the mean value.

Hilz *et al*[19] studied the SSRs induced by electrical, thermal, acoustic and IG in volunteers and 13 patients with familial dysautonomia (FD). All modes except cold stimulation were successful in all volunteers with a suggestion of a decrease in amplitude at the feet with increasing age. Consistent with the small fibre neuropathy in FD, the thermal modes did not always produce a response in the patients, and four had negative IG responses despite electrically induced SSRs in all 11, but this reflects the superior sensitivity of IG compared with electrical stimulation in the detection of peripheral neuropathy. The only description of the technique for IG training was that the 'tested persons were asked to take a deep breath.' Testing intervals varied between 60 and 120 s. One conclusion was that 'SSR testing with electrical stimulus only is too insensitive to evaluate autonomic or afferent small fibre neuropathy.'

It would appear therefore that even the sophisticated modalities are associated with some problems, which points to the place for a qualitative rather than a quantitative approach that could also be adopted in settings across the globe in order to be able to realise the recommendations for sympathetic assessments in routine clinical examinations.[2] Such a device could be an ordinary ward three-channel ECG monitor, analogous to the single-channel ECG recorder used in the present study.

Latency
One criticism of the present technique is that the actuation of the event marker is not electronically linked, which limits the interpretation of the response latencies which were indeed rather variable in some cases in the present study. However, an early commentator on SSR latency deduced that most of the time lag relates to postganglionic unmyelinated axonal conduction.[17] This author and Shahani studied patients with peripheral neuropathy and noted that whenever the SSR amplitude had been preserved, the latency was not different from normal. On the other hand, latencies in the able bodied show a considerable variance whatever the stimulus type and typically there is a 10–20% standard deviation from the mean value, whether the stimulus be electrical, acoustic, magnetic or IG. Some of the variation is age related. In none of the studies in SCI in which latency was measured was this measure shown to add to the diagnostic or therapeutic value even though it was satisfying to record its value.

Latency after IG, thermal stimulus or acoustic stimulus was not measured in the paper by Hilz *et al*[19] for the reason that the EMG was not triggered by the stimulus.

Habituation and drug effects
Many authors have noted the variability of amplitude of the SSR, dependant especially upon level of anxiety, ambient temperature, resting skin resistance and habituation. A minimum of 90 s was recommended between inspiratory SSRs to prevent habituation,[5] and while other workers did not find habituation to the gasp response after only a 30 s pause they did observe habituation and a change in waveform on electrical stimulation.[16] Only in one study out of 12, in which the training technique was unclear and with possible counfounding by habituation, was there an absent ID SSR in two out of 66 volunteers.[6] In clinical practice, the absolute value of SSR is of less importance than the presence or absence of a response, and the present study found that the IG invariably produced an SSR in the neurologically intact unlike the VE response.

Caution is also required in patients prescribed anticholinergic medication including amitryptilene[20] according to another IG SSR study in volunteers, even though our patients on average doses of oxybutynin had good responses, since doses causing symptomatic dryness do markedly reduce SSR amplitude and the test would best be undertaken after omitting the day's dose.

Despite standardisation in Siepman *et al*'s[20] study, variability in the sympathetic outflow to the skin was recorded in the skin microcirculation using laser Doppler fluxmetry. The skin blood flow change forms the basis of the galvanic skin response and this presents the possibility of recording from sites other than the palms and soles which are electrodermally more negative than skin with fewer sweat glands (-40 mV) with respect to other skin surface by virtue of the sweat glands there. Two studies have attempted to define the cord levels at which the palmar response is preserved, between T4 and T6, and at which the plantar response is preserved (below T8).[3,9] The GSR induced by the gasp reflex offers the possibility of examining the skin responses in a continuum between these levels[21] and merits further investigation.

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