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Autonomic dysfunction in elderly bedfast patients

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Abstract

Objective: to quantify autonomic function in bedfast elderly patients.
Patients and methods: we analysed orthostatic blood pressure, heart rate response to tilt, heart rate response to deep breathing, quantitative sudomotor axon reflex test (QSART) and beat-to-beat blood pressure during phases II and IV of the Valsalva manoeuvre (VM) in 15 patients with (OH+) and without orthostatic hypotension (OH−) and 12 age-matched controls.
Results: all bedfast patients had a poor response in the late phase II of beat-to-beat blood pressure, while OH+ patients had an additional abnormality in phase IV. QSARTs in the distal leg and foot were decreased in both OH+ and OH− groups. There was no difference between the two groups in duration of being bedfast or in activities of daily living.
Conclusions: (i) being bedfast results in postganglionic sympathetic dysfunction in the lower extremities; (ii) some patients who have β-adrenergic dysfunction have OH and (iii) preventing patients from becoming being bedfast may be important for the maintenance of normal autonomic functions.

Keywords: *autonomic dysfunctions, bedfast, orthostatic hypotension, quantitative sudomotor axon reflex test, Valsalva manoeuvre*

Introduction

When a subject assumes an erect posture, sympathetic activity causes a rise in heart rate and vasoconstriction. Failure of the circulatory reflex can lead to orthostatic hypotension—a reduction in blood pressure on standing—which can result in syncope or unsteadiness. Orthostatic hypotension could lead to an increased risk of brain damage through impaired cerebral autoregulation [1]. Vasoconstriction in the lower extremities plays a key role for this circulation reflex and thus an elastic stocking can be an effective treatment for orthostatic hypotension [2]. Orthostatic hypotension is associated with many conditions, including pure autonomic failure, multiple system atrophy, Parkinson's disease and being bedfast. However, the aetiology of orthostatic hypotension is poorly understood [3].

Beat-to-beat blood pressure alterations in response to Valsalva manoeuvre have been divided into four phases [4]. Phase I consists of a brisk rise in systolic and diastolic arterial pressure and a decrease in heart rate immediately after the onset of the strain, lasting around 4 s. Phase II consists of an early fall of arterial pressure followed by a late recovery (phase II-I). This progressive recovery of arterial pressure during phase II reflects a progressive increase in the total peripheral resistance. This is due to heightened sympathetic vasoconstrictor activity, as reflected by increased efferent sympathetic nervous outflow to limb muscles and is abolished by α-adrenergic blockade using phentolamine in young subjects [5]. Phase III is mechanical and is the mirror image of phase I. In phase IV, venous return to the heart, left ventricular stroke volume and cardiac output return towards normal, but the arteriolar bed remains vasoconstricted. This combination results in an overshoot of arterial pressure above control values. The overshoot of arterial pressure in phase IV is abolished by β-adrenergic blockade with propranolol [5].

We have focused on bedfast patients because, in Japan, the number of bedfast patients is increasing and thus the care of these patients is becoming more important [6]. We hypothesize that being bedfast not only causes muscle atrophy but also may result in dysfunction of the postganglionic sympathetic nerve causing impairment of vasoconstriction in the lower extremities. In this study we have investigated autonomic function to standing, Valsalva manoeuvre and

quantitative sudomotor axon reflex test (QSART) in elderly bedfast patients.

Materials and methods

Patients

Autonomic studies were performed on 15 bedridden patients who met the criteria of the Japanese Ministry of Health and Welfare's definition of bedfast (restricted to staying in bed for more than 6 months but able to assume a sitting position to take a meal) [7]. We measured haemoglobin, total protein and serum electrolyte concentrations to determine whether the patients were dehydrated and recorded the Barthel index and Functional Independence Measure.

The mean age was 85.1 ± 2.1 years (mean ± SE) and there were six men and nine women. Twelve patients had recurrent cerebral infarction and three had a complex fracture of the femur. None of them had diabetes mellitus or other diseases associated with autonomic neuropathy. No patients had severe dementia but some had minor impairment of recent memory. None was taking medications, such as nitrates, antidepressants or anticholinergic drugs, which cause orthostatic hypotension or sweat disturbance,

We performed the same autonomic testing on 12 age-matched healthy control subjects (five men, seven women). They were on no medication and their mean age was 81.3 ± 2.1 years.

Autonomic test

Autonomic function tests were performed in the morning using the methods of Low [8]. Before the test, we confirmed that no patient was pyrexial. The room temperature was maintained at 23°C and humidity was controlled.

Heart rate responses to deep breathing and the Valsalva manoeuvre

Heart rate was continuously recorded via electrocardiogram leads connected to a cardiac monitor (Dyna Scope; Fukuda Denshi). Systolic (SBP), diastolic and mean blood pressures (MBP) were continuously monitored using a photoplethysmographic technique (Finapres monitor, Ohmeda, Englewood, CO, USA). An inflatable cuff, containing the transducer of an infrared transmission plethysmograph, is wrapped around the middle phalanx of a finger and, by means of an active servo null mechanism, a counterpressure is generated whose value faithfully reproduces the blood volume pulsation under the cuff.

For heart rate responses to deep breathing, the patients breathed deeply at a rate of 6 cycles per min. Eight cycles were recorded. The five largest responses were read from the computer (NEC98) using a cursor, averaged and used to derive the heart rate range (maximum-minimum).

For the Valsalva ratio, the patients, rested and recumbent, were asked to maintain a column of mercury at 40 mmHg, for 15 s via a bugle with a small air leak. The patients were instructed to breath normally after the expiratory effort and were allowed to rest for at least 3 min after stabilization of arterial pressure and heart rate before repeating the manoeuvre. The Valsalva ratio is the ratio of the maximal to the minimal heart rate in response to the Valsalva manoeuvre. Beat-to-beat blood pressure response to the Valsalva manoeuvre were recorded and each of the phases quantified.

Orthostatic blood pressure recordings

Blood pressure recordings were measured simultaneously with a sphygmomanometer cuff and with a continuous non-invasive blood pressure monitor (Finapres monitor) to monitor beat-to-beat blood pressure. Blood pressure was measured in the supine position after a stable resting baseline was obtained, after which the patient was tilted upright to an angle of 80° for 5 min and then tilted back.

QSART

A population of eccrine sweat glands is stimulated by the iontophoresis of acetylcholine using a constant current generator (Asahi Denshi Co, Osaka, Japan) to produce a stimulus of 2 mA for 5 min. Impulses pass antidromically along sympathetic C fibres to a branch point then travel orthodromically along other sympathetic C fibres to evoke a sweat response with a latency of 1-2 min. Sweat output from a different compartment is evaporated by a stream of nitrogen gas of low constant humidity and controlled flow rate and measured by a sudorometer (Hidrograph; K&S, Aichi, Japan). The recording was continued for 5 min beyond the stimulus. The response was recorded over the left distal leg and proximal foot.

Statistical analysis

Data were compared using the unpaired group *t*-test (Welch method).

Results

Orthostatic hypotension

The patients were divided into orthostatic hypotension positive (OH+) and negative (OH−) groups according to the results of the tilt test at 1 min (Table 1). The OH+ patients had an orthostatic reduction in SBP of >30 mmHg or MBP >15 mmHg ($n = 6$; two men, four women; age 84.2 ± 2.3) and the OH− patients

Table 1. Postural changes in mean arterial blood pressure (MBP) and heart rate at 1 and 5 min in bedfast patients and in control subjects

	1 min		5 min	
	MBP	Heart rate	MBP	Heart rate
Controls	4.8 ± 3.1	12.6 ± 3.5	5.9 ± 2.5	9.9 ± 2.6[b]
Patients				
OH+	−21.0 ± 3.3	4.3 ± 2.9[a]	1.2 ± 6.2	7.2 ± 2.6
OH−	9.4 ± 6.0	17.3 ± 2.2	28.1 ± 6.1	18.4 ± 4.8

OH+, with orthostatic hypotension; OH− without orthostatic hypotension.
Comparison with OH- group [a]$P<0.010$; [b]$P<0.05$.

exhibited an orthostatic reduction in SBP of <30 mmHg or MBP <15 mmHg ($n=9$; four men, five women; age 85.7 ± 3.3). There was no significant difference in duration of being bedfast between the OH+ (25.5 ± 3.4 months) and OH− (36.1 ± 7.6) groups. The diagnostic categories in the OH+ group were recurrent cerebral infarctions (five cases) and femur fracture (one). In the OH− group they were recurrent cerebral infarction (seven cases) and femur fracture (two cases).

The Barthel index was higher in the OH+ group (23.3 ± 10.0) than in the OH− group (17.8 ± 6.6), but the difference was not significant. Neither was there any significant difference in Functional Independence Measure between OH+ (56.7 ± 11.7) and OH− (47.9 ± 7.6).

In the heart rate response to standing for OH+, OH− and controls, the tachycardia initiated by standing showed only in OH− at 1 and 5 min and there was a significant difference between OH− and OH+ ($P<0.01$). In the MBP response to standing after 5 min, both the OH+ and OH− groups partially recovered; however, the value in OH− (18.7 mmHg) was larger than OH+ (10.8 mmHg). There were no differences in haemoglobin, total protein and serum electrolyte concentrations between the OH+ and OH− groups.

Valsalva manoeuvre

As Figure 1 shows, beat-to-beat blood pressure alterations in response to the Valsalva manoeuvre followed a characteristic pattern in normal controls. Phase I consisted of a blood pressure increment lasting 2-4 s. Phase II was biphasic, consisting of an early decline interrupted by a rise in blood pressure, after 5 s, to above resting value (phase II-l). Phase III, the reciprocal of phase I, interrupted phase II and, after termination of the Valsalva manoeuvre, was followed by a sustained blood pressure overshoot. Mean blood pressure alterations for phases II-l and IV were −2.9 ± 2.7 and 21.3 ± 0.9, respectively.

The OH+ group was characterized by an excessive fall in blood pressure in phase II-l and a decrease of phase IV. Mean blood pressure value for phase II-l and IV were −11.7 ± 2.7 and 8.5 ± 4.1, respectively. The OH− group had an excessive fall in blood pressure in phase II-l but normal overshoot in phase IV. Mean blood pressure alterations during phase II-l and phase IV were −14.2 ± 3.9 and 23.0 ± 1.8, respectively. The value of phase II-l was significantly reduced in each of the groups when compared with controls. However in phase IV, there was a significant difference between OH+ and controls ($P<0.01$). There was also a significant difference between OH+ and OH− in phase IV ($P<0.05$).

Heart period response

The heart period responses to deep breathing for OH− (2.1 ± 0.3; beat/min), OH+ (3.3 ± 1.0) and controls (3.4 ± 1.4) were very similar (Table 2), as were the Valsalva ratios for OH− (1.2 ± 0.04), OH+ (1.2 ± 0.07) and controls (1.3 ± 0.03).

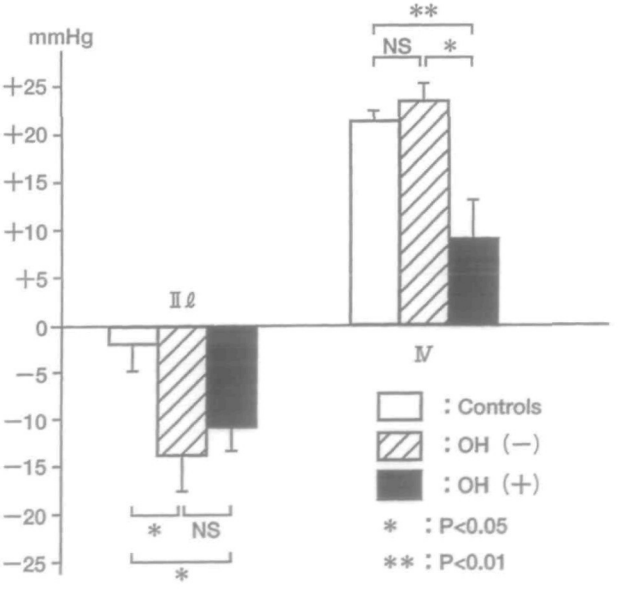

Figure 1. Mean arterial blood pressure changes during late phase II and phase IV of the Valsalva manoeuvre.

Table 2. Heart rate response to deep breathing and Valsalva ratio in bedfast patients and in control subjects

	Mean ± SE	
	Heart rate	Valsalva ratio
Controls	3.4 ± 1.4	1.3 ± 0.03
Patients		
OH+	3.3 ± 1.0	1.2 ± 0.07
OH−	2.1 ± 0.3	1.2 ± 0.04

OH+, with orthostatic hypotension; OH− without orthostatic hypotension.

QSART

QSART output was 0 and 0.01 ± 0.01 ml/cm^2 for the distal leg of OH+ and OH− respectively (Table 3). There was a significant difference among OH+, OH− and controls (0.81 ± 0.37). QSART was absent in the foot of OH+ and OH− and the control mean value was 0.55 ± 0.29.

Discussion

Bedfast patients had a poor response in the late phase II of beat-to-beat blood pressure during Valsalva manoeuvre, but only OH+ patients had additional abnormalities of phase IV. The tachycardia initiated by standing was present in only the OH− patients. QSART in the distal leg and foot was markedly decreased in both the OH+ and OH− groups. There was no difference between OH+ and OH− patients in duration of being bedfast or in activities of daily living.

Patients with orthostatic hypotension with attenuated heart rate responses, indicating widespread α- and β-adrenergic failure, exhibit the well-recognized pattern of blocked phase II and IV pressor responses. Patients without orthostatic hypotension, but who presumably have α-adrenergic failure, have a reduced phase II. These results suggest that being bedfast results first in α-adrenergic dysfunction, which might be partly due to muscle atrophy in the lower extremities, and later in β-adrenergic dysfunction. Sandoroni *et al.* pointed out that alterations in late phase II provide an early predictor of adrenergic impairment [5]. Patients without orthostatic hypotension might have compensatory hyper β-adrenergic function because phase IV was increased rather than reduced. Sandoroni *et al.* also observed the same phenomenon after α-blockade (phentolamine administration) [5]. Robinson *et al.* reported that tachycardia initiated by standing was present in elderly OH+ and OH− patients [1]. However, we observed more tachycardia in the standing position in the OH− group. Moreover at 5 min standing, the OH− group showed greater improvement. These results might be due to compensatory mechanism in β-adrenergic function and orthostatic hypotension may proceed by a slightly different mechanism in bedfast patients than in other elderly subjects. Cox *et al.* reported that β-blockade had been effective in treating some cases of neurocardiogenic syncope [9]. However, our results indicate a need for careful consideration before using β-blockade in patients with orthostatic hypotension who are bedfast. The mechanism of β-dysfunction in patients with orthostatic hypotension who are bedfast is complicated because there is no relationship between the duration of being bedfast, activities of daily living and the late phase II. Part of the reason is that phase IV is controlled by the cardiac adrenergic fibres which are primarily vagal [4] and therefore muscle atrophy in the lower extremity does not directly involve the vagus nerve. Some hormonal factors also influence this phenomenon.

Table 3. Quantitative sudomotor axon reflex test (QSART) on distal leg and the foot in bedfast patients and in control subjects

	QSART (mean ± SE)	
	Distal leg	Foot
Controls	0.81 ± 0.37	0.55 ± 0.29
Patients		
OH+	0	0
OH	0.01 ± 0.01	0

OH+, with orthostatic hypotension; OH− without orthostatic hypotension.

The QSART response is thought to be mediated by an axon reflex involving postganglionic sympathetic sudomotor fibres and their effector, the eccrine sweat gland. A normal test indicates integrity of the postganglionic sympathetic sudomotor axon. An absent or reduced response indicates a lesion of the postganglionic sudomotor axons [10]. Being bedfast might cause postganglionic sudomotor dysfunction in the lower extremity since both the OH+ and OH− patients had QSART abnormalities. Our Valsalva manoeuvre and QSART data suggest that being bedfast causes peripheral sympathetic dysfunction in the lower extremity.

With regard to Valsalva ratio results, we found no difference between the OH+, OH− and control patients. The Valsalva ratio has been widely used as a test of cardiovagal and baroreceptor function. However, Valsalva ratio is complicated because it does not solely depend on cardiovagal function but also on many other factors such as arterial pressure alterations, heart rate and the pooling and buffering effects of the thoracic vessels [4]. Since it also shows a clear

age-related impairment [11], our results may also be influenced by ageing.

Autonomic function declines with age [3]. Our results suggest that bedfast patients with orthostatic hypotension were most affected by peripheral sympathetic denervation in the lower extremity and by β-adrenergic dysfunction. However, the ageing process, underlying disease and neuro-hormonal abnormalities must be considered when interpreting these results.

Although the number of patients studied is too small to make definite conclusions, we suggest that being bedfast causes postganglionic sympathetic dysfunction in the lower extremities. Some patients, who also have β-adrenergic dysfunction, develop orthostatic hypotension. Preventing older people from becoming bedfast is important for maintaining activities of daily living; it may also prevent autonomic dysfunction.

Key points

- Autonomic function declines with age.
- In this small study, bedfast patients had reduced postganglionic sympathetic activities in the lower limbs compared with controls.
- The mechanism of orthostatic hypotension in bedfast patients is poorly understood.

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