Testing for autonomic neuropathy: heart rate changes after orthostatic manoeuvres and static muscle contractions

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Summary

1. The initial heart rate (HR) response evoked by standing, 70° head-up tilt, handgrip and contraction of abdominal and leg muscles was analysed in diabetic patients with autonomic neuropathy and in matched controls.

2. In healthy subjects standing induced an immediate, large, HR increase lasting 20 s that far exceeded the small HR rise induced by tilt. The HR response with handgrip and to contraction of abdominal and leg muscles was strikingly similar for the first 5 s to the HR increase after standing.

3. In diabetic patients handgrip and standing induced a small HR increase starting after 2–3 s. Contraction of abdominal and leg muscles evoked little or no HR changes. The HR rise after tilt up was delayed by 10 s compared with healthy controls.

4. It is concluded that the circulatory response to active and passive changes of posture differs fundamentally. Standing and handgrip are superior to head-up tilt as a test for vagal HR control. An abrupt and large HR increase after standing excludes cardiac parasympathetic neuropathy. A modified response, however, may be due to afferent as well as to efferent lesions, e.g. in muscle afferents or in vagal afferents from cardiopulmonary receptors.

Key words: diabetic autonomic neuropathy, vagal heart rate control, standing, tilt, handgrip, afferent mechanisms.

Introduction

The heart rate (HR) response evoked by standing exhibits a characteristic time course [1–6]. The magnitude of the initial HR changes is used to screen diabetic and other patients for cardiac parasympathetic neuropathy [2–7]. A controversy has arisen whether active or passive changes of posture are superior as tests for cardiac vagal neuropathy [8–13]. The controversy illustrates the poor understanding of the afferent mechanisms involved in the reflex HR response to active and passive arising. We re-examined the issue by comparing the instantaneous HR changes evoked by standing, 70° head-up tilt, handgrip and contraction of abdominal and leg muscles in diabetics with established cardiac vagal neuropathy and in healthy controls.

Methods

Five insulin-dependent diabetic patients were investigated. Severe impairment of vagal HR control was established by a markedly reduced HR variation on deep breathing [4, 5]. No drugs that influence the cardiovascular system were used. These patients were compared with five healthy age- and sex-matched controls (Table 1).

Examinations were performed in the morning, at least 1 h after the last meal and insulin injection. All subjects abstained from coffee and cigarettes on the day of the investigations. The instantaneous HR was determined from the electrocardiogram by a cardiotachometer and written on a pen recorder (Servogor RE511) running at a paper speed of 2 mm/s with a sensitivity of 2 mm/beat per min. A push-button-
activated event marker identified onset and duration of the manoeuvres listed below. Subjects rested in a supine position for at least 5 min before measurements were started. The resting HR was taken as the mean value over a 30 s period preceding the following tests:

(a) Standing.
(b) 70° head-up tilt on a tilt table with foot support and anti-slip mattress. A 70° tilt angle was chosen to avoid alarm reactions associated with the fear of or sensation of falling forward. At 70° tilt the gravitational influence on the circulation is only 6% less than in the vertical posture [6, 14]. Subjects were instructed to avoid straining of muscles during the tilt as much as possible, but were not strapped to the tilting table.

Standing and head-up tilt were accomplished in 3–5 s.
(c) Handgrip at maximal voluntary force during 5 s.
(d) Contraction of abdominal and leg muscles was performed in order to simulate the use of muscles involved in standing [6]. The manoeuvre was performed by lifting head and legs a few cm from the tilt table for 5 s.

Standing and muscle contractions were initiated on verbal command. A correction of 1 s was made to allow for the reaction time of the subject and the fact that the cardiotachometer lagged by one cardiac cycle [6].

Each test was performed five times. Sufficient time elapsed (2 min) between each of the various runs for HR to return to baseline values. Reproducibility of the tests was excellent, as shown previously [6]. The median HR response was determined at 1 s intervals and expressed as percentage deviation from the resting HR. Group results were plotted as average HR change (AHR, in %) at 1 s intervals. It is estimated that the error due to inaccurate readings from the pen recorder was \( \leq 1 \text{ beat/min} \) and \( \leq 1 \text{ s} \).

Arterial pressure was measured by the cuff method at rest and after 1 min in the erect posture.

One control subject was studied after blockade of parasympathetic HR control after intravenous administration of atropine (0.04 mg/kg).

Intra-arterial blood pressure was measured in one 47-year-old male insulin-dependent diabetic patient with autonomic neuropathy. A 28-h continuous intra-arterial ambulatory blood pressure registration was performed in this patient with the Oxford–Medilog system [15] in order to evaluate hypertension and presumed orthostatic hypotension. The investigative procedure was approved by the hospital ethical committee.

Intra-arterial pressure was measured in the left brachial artery at the level of the left ventricle. The test protocol was performed at the end of the 24 h ambulatory registration. Standing and tilt-up were performed five times as described above. The start of active and passive changes of posture were marked on the cassette tape and the pen recorder with the same push-button-activated event marker. Tape recordings were replayed at 25 times recording speed and the blood pressure signal was displayed on an Elema–Schonander ink-jet recorder at a paper speed of 50 mm/s, with a sensitivity of 1 mm/5 mmHg. The median HR and blood pressure response of five measurements was determined at 1 s intervals.

Statistics

Results are expressed as means \( \pm \text{ SEM} \). The unpaired Student t-test was applied to compare diabetics with controls, and the paired t-test to compare active and passive changes of posture:

| Table 1. Mean age, resting heart rate (HR), systolic and diastolic blood pressure (BP) and heart rate variation on deep breathing in diabetic patients and controls |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Age             | Sex             | Resting HR     | Resting systolic BP |
|                 | (years)         |                 | (beats/min)    | (mmHg)           |
| Controls (n = 5)| 3 ♀ 2 ♂         | 45 ± 7          | 65 ± 3         | 122 ± 7          |
|                 | Range 32–63     | Range 54–70     | Range 100–135  | Range 55–80      |
| Diabetics (n = 5)| 3 ♀ 2 ♂        | 43 ± 6          | 82 ± 4         | 154 ± 8          |
| P value         | N.S.            | \( P < 0.02 \)  | \( P < 0.002 \) | N.S.            |
|                 |                 |                 |                 | \( P < 0.005 \)  |
Heart rate response to standing and head-up tilt

Results

In the diabetic subjects supine HR and systolic blood pressure were higher than in controls (Table 1). Four diabetic subjects had an orthostatic fall of systolic pressure (>30 mmHg) after 1 min of standing.

Standing (Fig. 1a)

In controls, standing up evoked within 1 s an abrupt HR rise, that reached a maximum of 30 ± 6% at t = 11 ± 1 s after the onset of arising. HR decreased afterwards to a minimum of 11 ± 4% at t = 21 ± 1 s and increased afterwards gradually to 20 ± 4% at t = 60 s. In contrast, in the diabetic subjects the latency of the HR rise was prolonged (mean 3, range 2–5 s) and the temporary large HR increase was absent (Fig. 1a). At t = 11 s HR had increased by 4 ± 1%, at t = 21 s by 6 ± 1%, and at t = 60 s by 9 ± 1% (P < 0.005, P < 0.05 and P < 0.05, respectively, vs controls).

Handgrip (Fig. 1b)

In controls, HR increased within 1 s and reached a maximum of 24 ± 3% at t = 4 ± 1 s (P > 0.05 vs standing up). HR returned quickly to baseline values afterwards, in contrast with the further rise of HR observed after standing. In diabetics handgrip resulted after 3 s (range 1–5 s) in a small and sluggish HR increase, that reached a maximum of 4 ± 1% (P < 0.001 vs controls) at t = 9 ± 1 s.

![Figure 1](image_url)

FIG. 1. Average HR changes in five diabetics with cardiac vagal neuropathy (-----) and five healthy age-matched subjects (--), induced by standing (a), handgrip at maximal voluntary force (b), contraction of abdominal and leg muscles (c) and 70° head-up tilt (f). Atropine (-----) abolished the initial HR response by standing and handgrip in one healthy subject (d, e).
Contraction of abdominal and leg muscles (Fig. 1c)

In controls, HR increased within 1 s and reached a maximum of 20 ± 2% at t = 8 ± 1 s. HR continued to increase after the end of the straining of abdominal and leg muscles, in contrast with the fast HR fall at the end of handgrip. In diabetics contraction of abdominal and leg muscles evoked a very small and delayed HR response. No HR increase was noted in two patients.

Parasympathetic blockade (Figs. 1d and 1e)

Atropine completely abolished the instantaneous fast HR response evoked by standing and handgrip. A gradual rise of HR remained that started after 1 s.

Head-up tilt (Fig. 1f)

In controls HR rose gradually, starting after >1 s, to 5 ± 2% at t = 11 s, to 8 ± 3% at t = 21 s, and to 17 ± 3% at t = 60 s (P < 0.005, P > 0.05 and P > 0.05, respectively, vs standing up). In diabetics the onset of the HR rise was delayed by 10 s compared with controls (Fig. 1f). At t = 11, 21 and 60 s HR was 0 ± 1%, 2 ± 1% and 7 ± 2% (P < 0.02, P < 0.005 and P > 0.05, respectively, vs standing up). The HR increase after 60 s tilt up in diabetics was less than in controls (P < 0.05), but the HR changes after 11 and 21 s tilt up were not significantly different between diabetics and controls.

Blood pressure response

Fig. 2 shows the divergent cardiovascular responses to standing (a) and head-up tilt (b) in a diabetic patient with autonomic neuropathy.

Discussion

The reflex HR rise with active and passive changes of posture differed distinctively for approximately 20 s, both in healthy subjects and in patients with diabetic autonomic neuropathy. Fig. 1 indicates that both standing and handgrip are superior to head-up tilt as tests for vagal HR control, because atropine blocked the greatest part of the large initial HR increase on standing (Fig. 1d) [2, 3] and handgrip (Fig. 1e) [16, 17]. With head-up tilt the initial HR response does not discriminate between parasympathetic cardiac neuropathy and normal HR control (Fig. 1f).

Recently we have described the mechanisms of the initial HR response to standing [6]. The immediate, primary HR increase on standing is due to the exercise reflex. The secondary, more gradual HR increase after 5 s standing, and the subsequent rapid decrease between about 12 and 20 s, correspond through the baroreceptor reflex to a striking fall, recovery and sometimes overshoot of arterial pressure. In contrast with standing, 70° head-up tilt induces a gradual small increase in blood pressure and heart rate. It was concluded that active and passive changes of posture result in fundamentally different cardiovascular effects for about 20 s [6]. The present results confirm and extend our previous findings. The three manoeuvres which involved contraction of skeletal muscles (Figs. 1a–1c) evoked a similar fast HR rise for the first 5 s. Afterwards the HR changes depended on the muscles used: HR quickly returned to baseline values after handgrip, but continued to rise after straining the
muscles involved in standing. The algebraic sum of contraction of abdominal and leg muscles (Fig. 1c) and tilt-up (Fig. 1f) was similar to the HR changes induced by standing (Fig. 1a). Thus the muscular effort of standing up (Figs. 1a and 1c), rather than the change of posture (Fig. 1f), is responsible for the characteristic initial HR response to standing.

Rapid head-up tilt is probably accompanied by involuntary muscle contractions due to the sensation of falling forward [11]. Consequently the biphasic HR changes that Sundkvist et al. [10, 12] and Duncan et al. [8] reported after rapid head-up tilt seem to be comparable with a more gradual tilt combined with some straining of abdominal and leg muscles [6].

Contraction of abdominal and leg muscles evoked little or no HR changes in diabetics (Fig. 1e), whereas handgrip induced a small but significant HR increase (Fig. 1b), owing to augmentation of sympathetic tone (Fig. 1e). This may be attributed to an earlier involvement of muscle afferents (peripheral neuropathy) in the lower than in the upper extremities [18].

Standing induced an immediate blood pressure jump lasting about 1 s and a distinct fall and recovery of arterial pressure that was not present after head-up tilt (Fig. 2). These changes resemble the circulatory response to standing in healthy controls [6]. However, the blood pressure changes in Fig. 2 were not accompanied by baroreflex-mediated HR changes.

The mechanisms of the initial HR response to standing are complex. Muscle receptors, high-pressure receptors, low-pressure receptors and the plasma catecholamine level are probably all involved [6]. The gradual HR rise induced by passive head-up tilt (Fig. 1f) is attributed to unloading of cardiopulmonary and carotid sinus baroreceptors [14, 19]. Brief muscle contractions [16, 17] and changes of systemic arterial pressure [20] influence HR predominantly by modulation of vagal tone. In contrast, changes of thoracic blood volume modulate both divisions of the autonomic nervous system [14, 19, 21].

Basic to the interpretation of impaired HR responses in diabetics (Figs. 1 and 2) is the markedly different latency and time constant for the heart's response to the two neurotransmitters [22, 23]: vagally mediated HR changes have a latency of a few hundred milliseconds and a time constant of a few seconds, whereas these values are 1–3 s and about 10 s, respectively, for sympathetically mediated effects (cf. Figs. 1d and 1e). In the diabetic group parasympathetic cardiac neuropathy was established by an almost absent HR variation on deep breathing (Table 1). The HR response to standing and handgrip confirmed that vagal HR control was completely lost.

Sympathetic HR control was partially intact, as indicated by the sluggish HR rise starting 2–3 s after standing and handgrip (compare Figs. 1a and 1d, 1b and 1e, and 2). Consequently, the extremely long latency (>10 s) for the HR rise with head-up tilt in diabetics (Figs. 1f and 2b) has to be ascribed to afferent lesions in addition. The present findings suggest possible neuropathy of vagal afferent fibres from cardiopulmonary receptors [19].

In conclusion, standing up is superior to head-up tilt as a test for vagal HR control. An abrupt and large HR rise on standing excludes vagal neuropathy. However, the origin of the initial HR response to standing is complex [6]. A delayed or otherwise modified HR response may be due to neuropathy of efferent and/or afferent reflex pathways, e.g. to lesions in muscle afferents or in vagal afferents from cardiopulmonary receptors.

References


