Effects of head-up tilting on baroreceptor control in subjects with different tolerances to orthostatic stress

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ABSTRACT

During orthostatic stress, an increase in peripheral vascular resistance normally results in arterial blood pressure being well maintained, despite a decrease in cardiac output. The present study was undertaken to determine whether the sensitivity of the carotid baroreceptor reflex was increased during orthostatic stress and whether failure to develop this increase was associated with poor orthostatic tolerance. Three groups of subjects were studied: asymptomatic controls; patients investigated for suspected posturally related syncope but who had normal responses to an orthostatic stress test (normal patients); and patients who were shown to have low orthostatic tolerance (early fainters). We determined responses of R–R interval and forearm vascular resistance (mean arterial pressure/brachial artery velocity by Doppler ultrasonography) to the loading and unloading of carotid baroreceptors by application of pressures of −30 and +30 mmHg to a chamber fitted over the neck. Responses were determined after 20 min of supine rest and after 10 min of head-up tilt at 60°. Responses of cardiac interval were not significantly different between the three groups, and they were not altered by the postural change. Vascular responses also did not differ between the groups during supine rest. However, in healthy volunteers and in normal patients, responses to both neck suction and pressure were significantly enhanced during head-up tilt. In controls, responses to suction were increased by tilt from 0.04 ± 0.1 to −1.01 ± 0.2% · mmHg⁻¹ (means ± S.E.M.; P < 0.001) and those to neck pressure from −0.6 ± 0.3 to −3.1 ± 1.1% · mmHg⁻¹ (P < 0.05). In the normal patients, the corresponding changes were: during suction, from −0.2 ± 0.1 to −0.7 ± 0.1% · mmHg⁻¹ (P < 0.05); during pressure, from −0.7 ± 0.1 to −1.5 ± 0.3% · mmHg⁻¹ (P < 0.05). In contrast, in patients with low orthostatic tolerance, posture had no effect on the reflex (neck suction, from −0.3 ± 0.1 to −0.3 ± 0.1% · mmHg⁻¹; neck pressure, from −1.0 ± 0.3 to −0.9 ± 0.2% · mmHg⁻¹). We suggest that an increase in the sensitivity of the carotid baroreceptor/vascular resistance reflex may be important in the maintenance of blood pressure during orthostatic stress, and that failure of this to occur in patients with posturally related syncope may go some way towards explaining their poor orthostatic tolerance.

INTRODUCTION

The baroreceptor reflex is known to be important in reducing variations in arterial pressure [1]. Carotid baroreceptors are likely to be of particular importance during postural changes in humans, due to the large alterations in their position relative to the heart. Patients with posturally related hypotension and syncope fail to maintain adequate blood pressure during orthostatic stress, and it is possible that inadequate baroreflexes may

Key words: baroreceptor reflex, head-up tilt, orthostatic stress, vascular resistance.
Abbreviations: LBNP, lower-body negative pressure.
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at least partly explain this deficiency. In support of this view, it has been shown that, following extended bed rest [2] or detraining [3], decreases in orthostatic tolerance were associated with reductions in baroreceptor sensitivity.

Most previous studies that have examined baroreceptor reflexes have concentrated on the cardiac responses; however, of much greater importance in blood pressure control are the responses of vascular resistance [4,5]. We have recently reported that in asymptomatic volunteers the sensitivity of the carotid baroreceptor control of forearm vascular resistance is increased during the simulated orthostatic stress achieved by application of lower body suction [6]. The present investigation was designed to examine the effects of orthostatic stress effected by head-up tilting on baroreceptor control not only of heart rate but more particularly of vascular resistance. The likely importance of this mechanism was assessed by comparison of the responses in three groups of subjects: asymptomatic volunteers, patients with a history of unexplained syncope but who had normal responses to an orthostatic stress test, and patients with previously demonstrated low orthostatic tolerance.

METHODS

Subjects
Tests were carried out on 40 consecutive patients (20 male) aged 16–72 years (median 36.5 years) who had been referred for orthostatic stress testing due to attacks of syncope or presyncope that were of unknown cause despite routine cardiological and neurological investigations. Investigations included resting ECG and 24 or 48 h recordings (all patients), and exercise ECG, ambulatory blood pressure monitoring and echocardiogram as requested by the referring physician. The frequency of attacks varied from five times per day to once a year (median 0.3 per week), and attacks had been occurring for periods of between 1 month and 40 years (median 4 years). Patients were admitted to the study only if they had no other known cardiovascular or neurological disorders. Studies were also undertaken using 12 asymptomatic volunteer subjects (six male) aged 22–60 years (median 30 years). The study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association, and was approved by the Research Ethics Committee of the United Leeds Teaching Hospitals.

Procedure
All tests were carried out in the morning in a temperature-controlled laboratory (22–24 °C). Subjects had been instructed to have only a light breakfast and to abstain from caffeine-containing beverages from the previous evening. After explanation of the procedures and signing of consent forms, subjects rested supine on a combined tilt/lower-body suction device. The subject’s right arm was supported in a position so that the forearm would remain at heart level at different positions of the tilting device. The following monitoring devices were attached: three-lead ECG, automatic sphygmomanometer (78325C; Hewlett Packard, Böblingen, Germany) and finger photoplethysmographic blood pressure monitor (Finapres; Ohmeda 2300). An 8 MHz Doppler ultrasound probe (Doptek, Chichester, U.K.) was positioned over the brachial artery and clamped firmly in position. Care was taken throughout the study to ensure that the position of the probe and its angle with the brachial artery remained constant.

Subjects remained resting in a supine position for a minimum of 20 min before experimental procedures were started. Responses of cardiac interval and of forearm flow and arterial blood pressure to the loading and unloading of carotid baroreceptors were determined. Subjects then remained supine for a further period of 20 min before being tilted head-up at an angle of 60°. After a further 10 min, carotid baroreceptor tests were repeated. After this the orthostatic stress test was continued to determine the subject’s orthostatic tolerance.

Carotid baroreceptor loading and unloading
This was performed using a neck chamber modified from the design described by Eckberg et al. [7]. Briefly, the chamber was made from sheet lead, which was cut and soldered to fit around the lateral and anterior aspects of the neck between the border of the chest, the lower border of the mandible and the posterior neck muscles. The border of the collar was covered with neoprene foam lined with an impermeable membrane. The collar was moulded to fit each subject individually, and held in place manually. The device was connected, via tubing, to a 10-litre reservoir, which in turn was connected to a vacuum source (industrial vacuum cleaner) that was able to produce both negative and positive pressures. The opening of a tap between the chamber and the reservoir allowed the rapid application of pressure change in the chamber. The neck chamber was connected via a nylon catheter to a pressure transducer (Gould Statham P23Gb) to record the applied pressure. To calibrate the transducer, it was connected to the reservoir and known pressures were applied.

Two protocols were used. Cardiac responses were assessed during held expiration to eliminate respiratory sinus arrhythmia. After a normal expiration, subjects held their breath for 10 s. After 5 s, neck suction (−30 mmHg) or neck pressure (+30 mmHg) was applied through the neck chamber. The three beats prior to the application of suction or pressure were taken as control, and the maximum prolongation (suction) or reduction (pressure) of R–R interval during stimulation...
was taken as the response. In the second protocol, vascular responses were assessed. Subjects were asked to breathe continuously; records were taken during a control period of 15 s, then for 20 s while neck suction or pressure was applied. The response was calculated as the maximum percentage change in forearm vascular resistance (mean arterial blood pressure/mean brachial blood velocity) during stimulation compared with control. All tests were performed twice while supine and once during tilt.

The responses of both pulse interval and vascular resistance were expressed as reflex sensitivity, calculated by dividing the response by the change in pressure recorded in the neck chamber.

Orthostatic stress test
This has been described previously in detail [8,9]. Briefly, the patient lay supine on the tilt table and was positioned on the table using an adjustable footboard so that the legs and the pelvic region were contained within the lower-body negative pressure (LBNP) chamber. The LBNP chamber consisted of a polypropylene cover fitted to the tilt table, with a seal completed by a plate lined with neoprene foam around the subject at the level of the iliac crest. The chamber was connected to a vacuum source and had a pressure gauge that was calibrated below atmospheric pressure. The test consisted of 20 min of supine rest, 20 min of head-up tilt at 60°, then head-up tilt combined with LBNP at −20, −40 and −60 mmHg for 10 min each or until the onset of presyncope. The test was then terminated and the subject returned to the supine position. Presyncope was recognized as a drop of systolic pressure below 80 mmHg and a feeling of dizziness. The measure of orthostatic tolerance was taken as the time from the start of head-up tilt until presyncope. The repeatability of this, assessed from repeated assessments, was better than ±2 min [8]. Values obtained from each subject were compared with previously published reference data [8]. The reference data indicate the time and the stage of the orthostatic stress test at which presyncope occurs in 20% of asymptomatic control subjects. Values are age- and sex-related.

Statistical analysis
Values are reported as means ± S.E.M., unless otherwise stated. All values were tested for normality, and parametric or non-parametric tests were used as appropriate. Inter-group differences were assessed using either one-way ANOVA or the Kruskal–Wallis test where data were non-parametric. Differences between conditions within each group were assessed using either a paired Student’s t test or the Wilcoxon test for non-parametric data.

RESULTS
On the basis of their orthostatic tolerance, expressed as time to presyncope (min), the patients were divided into two groups. Those with times to presyncope that were lower than those predicted for age- and sex-matched controls [8] (26.0 ± 0.8 min; range 16–30 min) were designated the early fainters (n = 21). In this group there were eight males and 13 females, aged 19–72 years (median 37 years). The remaining 19 patients had orthostatic tolerances that were the same as or better than predicted (34.2 ± 0.8 min; range 31–40 min), and these were designated the normal patients. This group consisted of 12 male and seven female subjects, aged 16–61 years (median 34 years). The control group had a mean orthostatic tolerance of 35.6 ± 1.8 min (range 29–50 min), and all values were within normal limits.

Two patients in each group and three control subjects showed mixed cardio-inhibitory and vasodepressor responses. All other subjects showed a predominantly vasodepressor response.

Data obtained during supine rest and after 10 min of head-up tilt in the three groups of subjects are listed in Table 1. These results show that, after 10 min of head-up tilt, heart rate, mean arterial pressure and forearm vascular resistance increased significantly in all three groups. Forearm blood velocity was reduced in all three groups, but this was statistically significant only for the early fainters.

Cardiac responses to carotid baroreceptor stimulation
In all groups, both while supine and during head-up tilt, increasing baroreceptor stimulation by application of neck suction caused a prolongation of the cardiac interval, whereas decreasing the stimulus by application of neck pressure decreased the cardiac interval. In control subjects and normal patients, the calculated responses of baroreceptor sensitivity to neck suction tended to be greater during head-up tilt than when supine. However, this was a variable response and did not reach statistical significance (P = 0.069 in normal patients and P = 0.26 in controls). The responses in the various groups are compared in Figure 1.

Vascular resistance responses
The responses of vascular resistance parameters to changes in baroreceptor stimulation were measured as the peak responses; these occurred at 8.9 ± 0.2 s after the onset of the stimulus. The responses in both positions and in all three groups of subjects are shown in Figure 2. In the supine position, responses to suction (stimulation) were small in all groups, and responses to pressure,
Table 1  Cardiac and vascular resistance responses to head-up tilt in the three groups of subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control subjects</th>
<th>Normal patients</th>
<th>Early fainters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Tilted</td>
<td>Supine</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64.9 ± 2.7</td>
<td>78.0 ± 3.3***</td>
<td>62.4 ± 1.7</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>86.8 ± 1.0</td>
<td>92.4 ± 1.6**</td>
<td>87.7 ± 0.9</td>
</tr>
<tr>
<td>Forearm blood velocity (cm/s)</td>
<td>6.1 ± 0.7</td>
<td>3.8 ± 0.3</td>
<td>4.3 ± 0.7</td>
</tr>
<tr>
<td>Forearm vascular resistance (units)</td>
<td>20.1 ± 1.5</td>
<td>26.9 ± 3.7*</td>
<td>24.9 ± 0.9</td>
</tr>
</tbody>
</table>

Although larger than those to suction, did not differ between the groups. During head-up tilt, the vascular responses both to suction and to pressure were significantly enhanced in both control subjects and normal patients. In the early fainters group, however, responses during head-up tilt were not significantly changed from those during supine rest. In particular, the large response of vascular resistance to baroreceptor unloading that was seen in control subjects was not seen in the early fainters.

DISCUSSION

Orthostatic stress, due to maintaining a motionless upright posture, results in a decrease in the return of blood to the heart and a consequent decrease in cardiac output. The importance of the baroreceptors, particularly those in the carotid sinuses, in initiating compensatory reflex responses is undisputed. However, what is unclear is whether, in people with poor tolerance to orthostatic stress but no overt cardiovascular or neurological deficit, relatively low baroreceptor sensitivity is at least partly responsible for their attacks of syncope or near-syncope. Most previous work has concentrated on the baroreflex control of heart rate, whereas it is the control of vascular resistance that is of much greater importance in the maintenance of blood pressure during orthostatic stress. The present study has attempted to address this problem by determining, in normal subjects and in patients with and without orthostatic intolerance, both cardiac and vascular components of the carotid baroreceptor reflex, in both the supine and upright positions. The results have indicated that, although the cardiac responses seem to be equivocal, the much more important vascular responses were significantly enhanced in the upright position in subjects with good orthostatic tolerance, but were not enhanced in those with poor tolerance.

Cardiac responses

There have been several previous investigations of the effects of posture on the responses of heart rate to baroreceptor stimulation in normal subjects. The results are conflicting. Early studies which determined the effects of carotid baroreceptor stimulation reported no significant effects of posture [10,11] or simulated postural change using lower-body suction [12]. On the other hand, when baroreceptor sensitivity was assessed using phenylephrine injections, cardiac responses were found...
to be smaller when the subject was in the upright position compared with those when supine [13,14], and this was attributed to the lower level of vagal tone when upright. In contrast with that report, another study that examined the effects of lower-body suction found that this actually increased the cardiac responses to both neck suction and pressure [15]. Our results, measuring cardiac responses both to stimulation and to unloading of carotid baroreceptors, showed no consistent effects in any of our groups of subjects, although there was a tendency (not significant) for cardiac responses to be enhanced during orthostasis in the groups with normal orthostatic tolerance. The present results thus are comparable with the majority of previous reports of carotid baroreflexes.

**Vascular responses**

A major factor in the failure of the adequate maintenance of blood pressure during orthostatic stress is an inadequate response of peripheral vasoconstriction [16,17]. Since it is the baroreflex that is mainly responsible for initiating vasoconstriction, it is appropriate to examine whether poor tolerance to orthostatic stress is associated with small vascular responses to baroreceptor stimulation. We determined responses of vascular resistance in the forearm from changes in the ratio of brachial artery velocity to mean arterial pressure. This has been used in previous studies [6,17], and it provides a reliable estimate of the changes in resistance, provided that the angle of the Doppler probe in relation to the artery remains constant. Resistance responses were taken as the maximum change during the stimulus from the control. One potential disadvantage of studying the responses in such an ‘open loop’ preparation is that any responses would affect other reflexogenic areas and tend to buffer the resulting change. This effect, however, is likely to be relatively small because, rather than attempting to measure a steady-state response, we measured only the peak responses, which occurred 9 s after the application of the stimulus and before any major degree of buffering would be likely to have occurred.

The reflex vascular responses to both loading and unloading of the carotid baroreceptors were measured and we found that, in the supine position, there were no significant differences between the groups. Of greater interest, however, is the influence of posture on the baroreceptor/vascular reflex. We found that, when normal control subjects or patients with normal orthostatic stress test results were tilted, the responses to both carotid suction and pressure were significantly enhanced. In patients in whom orthostatic tolerance had been shown to be low, however, vascular responses were unaffected by posture. There have been no comparable previous studies, although Ebert [18] reported that, in normal subjects, lower-body suction increased the vasodilatation induced by neck suction. Previous reports from our laboratory [6,19] also indicated that the responses of vascular resistance in normal subjects to changes in neck collar pressure were enhanced by lower-body suction.

The mechanism that is responsible for increasing the vascular responses to baroreceptor stimulation during orthostasis in normal subjects is not known. One possible explanation is that it is related to higher levels of vascular resistance when the subject is upright. This would be relevant to responses to increases in baroreceptor stimulation, which would be expected to result in a greater decrease in resistance when the initial level was increased. This does not, however, explain the increased response to unloading of the baroreceptors. Various hypotheses have been put forward to attempt to explain the effects of posture or lower-body suction on baroreflexes. One favoured explanation is that the low-pressure receptors in the thorax inhibit the baroreceptor reflex, and that transfer of blood from the thorax lessens this inhibition [12,15,20–22]. Direct evidence for this, however, is lacking, as studies of discrete stimulation of various intrathoracic receptive areas have failed to show appropriate responses [23–25]. Another possibility that has recently been explored using an animal model is that distension of sub-diaphragmatic capacitance vessels could excite receptors, which then interact with baroreceptors to increase their sensitivity [26]. At present we can only speculate on the physiological mechanisms whereby the baroreceptor reflex is affected by posture. Although we have shown clear differences between the three groups of subjects with regard to enhancement of vascular responses to baroreceptor stimulation, we do not claim that failure of this is necessarily the only mechanism responsible for presyncope in the early fainting patients. Tolerance to orthostatic stress is dependent on several other factors, including plasma volume and physical fitness [27,28]. The extent to which any particular factor may be held responsible for orthostatic intolerance may also be dependent on the selection criteria, i.e. on the test used to assess orthostatic tolerance. We firmly believe that tests that employ invasive procedures or drug administration should be avoided, as they do not clearly separate the responses of fainting patients from controls [29,30]; this may explain, for example, why in one study follow-up data from tilt-positive and tilt-negative patients did not clearly differ [31]. The test that we use applies a purely physiological stress and determines the ability of each subject to tolerate this. Our results have shown clearly that the subjects (both controls and patients) who are better able to tolerate this orthostatic stress are the ones who show enhancement of the baroreceptor/vascular resistance response. The implication from our results is that this enhancement is likely to be an important factor in the response to gravitational stress, and that failure of this enhancement is likely to contribute to the occurrence of posturally related syncope.
Conclusion
The results of this study have indicated that, in the supine position, there were no significant differences in cardiac or vascular responses in the various groups of subjects to changes in stimulation of the carotid baroreceptors. However, in both normal subjects and patients with good orthostatic tolerance, the sensitivity of the reflex responses of vascular resistance were significantly enhanced when the subject was tilted upright. In patients with poor orthostatic tolerance, however, no such enhancement occurred. This failure of potentiation of the reflex may underlie, at least partly, the diminished tolerance of orthostatic stress of these patients.

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REFERENCES

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