Orthostatic blood pressure changes and arterial baroreflex sensitivity in elderly subjects

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Abstract

Background: orthostatic hypotension in elderly people is often attributed to diminished afferent baroreflex sensitivity, but this has not been demonstrated. We examined the hypothesis that postural change in blood pressure is related to baroreflex sensitivity, independent of the confounding effect of baseline blood pressure.

Methods: we studied 25 active, untreated elderly subjects free of postural symptoms (mean age 70 ± 1 years): 16 with hypertension (clinic blood pressure 194 ± 6/98 ± 3 mmHg) and nine normotensive controls (clinic blood pressure 134 ± 3/77 ± 3 mmHg). We assessed baroreflex sensitivity from the heart rate and blood pressure responses to the Valsalva manoeuvre and a pressor and depressor stimulus (bolus phenylephrine injection or sodium nitroprusside infusion respectively). Subjects were then passively tilted to 60° and maximum changes in systolic blood pressure, heart rate, forearm blood flow and forearm vascular resistance recorded.

Results: maximum change in systolic blood pressure with head-up tilt was correlated with supine systolic blood pressure (r = 0.60, P = 0.001). Maximum change in systolic blood pressure with orthostasis was greater in the hypertensive subjects (45 ± 4 mmHg versus 29 ± 6, P = 0.04) and the heart rate increment was less (16 ± 2 bpm versus 24 ± 4, P = 0.02). The increase in forearm vascular resistance with tilt was similar in the two groups (47 ± 11 versus 38 ± 7 units, P = 0.52). All three methods of assessing baroreflex sensitivity showed a reduction in the hypertensive subjects (all P < 0.02). Lower values of baroreflex sensitivity were related to greater falls in systolic blood pressure, heart rate, forearm blood flow and forearm vascular resistance recorded.

Conclusions: we found a relationship between baroreflex sensitivity and the systolic blood pressure fall with orthostasis, even after adjustment for prevailing systolic blood pressure. Despite equivalent changes in forearm vascular resistance with tilt, greater falls in systolic blood pressure were seen in hypertensive subjects than in normotensive controls, due in part to an inadequate baroreflex-mediated heart rate response. The postural fall in blood pressure often observed in elderly hypertensive subjects may be related to the reduced baroreflex sensitivity seen in this condition.

Keywords: aged, baroreflex, hypertension, nitroprusside, phenylephrine, pressoreceptors, tilt test

Introduction

A fall in blood pressure on standing is common in elderly subjects, with orthostatic hypotension [a fall in systolic blood pressure (SBP) of ≥ 20 mmHg or diastolic blood pressure (DBP) of ≥ 10 mmHg on standing] occurring in 6–30% of elderly people [1–3]. The maintenance of blood pressure and cerebral perfusion with postural change, and thus the avoidance of dizziness or syncope, depends on the action of baroreflexes to compensate for falls in central blood volume and stroke volume. A postural fall in blood pressure in elderly subjects may influence decisions about antihypertensive treatment, especially as there is an association between increasing supine SBP and increasing orthostatic blood pressure change [3–5]. This association is usually attributed to alterations in the baroreflex response evoked by postural change, which is attributed to arteriosclerosis [6, 7].

However, evidence for this link is limited or contradictory. One study of younger symptomatic subjects found that increased carotid baroreceptor-heart rate reflex sensitivity (BRS) was paradoxically associated with a reduction in orthostatic tolerance [8],
perhaps related to changes in plasma volume. Studies in elderly people have found either no relation between reduced arterial BRS and greater falls in SBP with tilting in hypertensive and normotensive subjects [9] or that the presence of orthostatic hypotension makes no difference to the heart rate response to standing [10]. Tonkin et al. [11] postulated a defect of the afferent limb of the baroreflex arc. This was based on their observation of an inadequate heart rate response to tilt in elderly subjects with age-associated orthostatic hypotension. However, their study contained no separate assessment of arterial BRS.

We have tested the hypothesis that postural change in blood pressure is related to BRS, independent of the confounding effect of baseline blood pressure. We have examined arterial BRS and the baroreceptor-vascular response to tilt in elderly subjects across a wide range of blood pressures.

Materials and methods

Study subjects

We studied 25 people aged over 60 (mean age 70 ± 1 years, range 60–76), of whom 12 were women. Sixteen were hypertensive subjects who had not previously received treatment (sustained clinic SBP ≥ 160 mmHg and/or DBP ≥ 90 mmHg) and nine were normotensive (sustained clinic BP < 160/90 mmHg). The hypertensive subjects were outpatients attending for assessment of hypertension. Normotensive subjects were spouses and friends of hypertensive subjects or respondents to a newspaper advertisement. All subjects were active and ambulant, living independently at home and with no postural symptoms or history of syncope. All were in sinus rhythm and had a normal electrocardiogram and normal fasting plasma glucose. Those with a history of other cardiovascular disease (including atrial fibrillation), other disorders associated with autonomic dysfunction or other major illness were excluded. Those taking medication with cardiovascular or autonomic effects were also excluded. All gave written informed consent. The study was approved by the local research ethics committee.

Clinic blood pressure was measured on three separate occasions at least 1 week apart, using a standard mercury sphygmomanometer and a cuff of the appropriate size. Supine blood pressure was recorded as the mean of three readings taken after a 5 min rest. We took standing blood pressure readings after 1, 2 and 3 min of standing and averaged the results for each visit. We calculated a final value for supine and standing blood pressure from the mean of these values.

Study protocol

Each subject attended the cardiovascular laboratory after a light breakfast, having emptied the bladder and having refrained from smoking and consuming alcohol and caffeine-containing products for at least 12 h. They wore light clothing. The laboratory temperature was kept constant between 20 and 22°C. Subjects rested supine for at least 30 min after the insertion of a cannula into a dorsal hand vein. Each subject was fitted with chest leads for the continuous surface electrocardiogram (CR7, Cardiac Recorders Ltd, London, UK) and with appropriately sized finger cuffs from the Finapres 2300 non-invasive beat-to-beat blood pressure recording device (Ohmeda Monitoring Systems, Englewood, CO, USA). The finger cuff was fitted to the middle finger or thumb of the non-dominant hand, which rested throughout on an adjustable support at the level of the heart to eliminate any hydrostatic effects.

Arterial BRS testing was then performed using three methods: the blood pressure and heart rate responses during the release phase of the Valsalva manoeuvre [12–15] and the responses to transient pressor and depressor stimuli (phenylephrine bolus injection and sodium nitroprusside infusion). These methods are described in detail elsewhere [14–17].

After being familiarized with the tilting procedure, subjects were manually tilted rapidly to 60° (the manoeuvre taking 3–5 s) while lightly strapped to a hydraulic tilt table fitted with foot support (Akron Medical Products, Ipswich, UK) and then held in that position for 3 min. We repeated this manoeuvre two more times and took the average of the three responses. During tilt, blood pressure and pulse interval were recorded as before, and forearm blood flow (FBF) was measured by venous occlusion plethysmography with a mercury-in-silastic strain gauge plethysmograph (Department of Medical Physics, Queen’s Medical Centre, Nottingham, UK). With this technique, the rate of change of circumference of the forearm during cyclical venous occlusion is proportional to blood flow into the limb. We recorded FBF for 1 min at baseline and during the 3 min of tilt, raising the arm attached to the FBF equipment on an adjustable support to retain the angle to the horizontal.

After a further period of supine rest, we recorded the blood pressure, heart rate and FBF responses to the application of a refrigerated gel pack (2–4°C) to the forehead for 45 s [18, 19]. Subjects wore protective glasses to avoid stimulation of the oculo-cardiac reflex. We took the average of two responses. At least 5 min elapsed between these tests to permit the recovery of baseline values for blood pressure and heart rate.

Data analysis

The values for BRS from the Valsalva manoeuvre were derived from the data from three Valsalva manoeuvres from the whole of phase 4, according to the method of Smith et al. [13]. Values for BRS derived from the
phenylephrine injection technique and the sodium nitroprusside depressor response were determined from the linear regression of pulse interval on blood pressure for the immediately preceding beat during the ‘ramp’ portion of the blood pressure response [14–16]. Values for each of the (minimum three) effective doses were averaged for each individual.

FBF is expressed as ml per min per 100 ml of forearm tissue, and the ratio of FBF to the mean arterial pressure prevailing during that cycle (taken from the simultaneous Finapres recording) was expressed in arbitrary units representing forearm vascular resistance (FVR). We considered FBF and FVR values at baseline and at 15, 30, 60, 90, 120 and 180 s after tilt. Thus, the final value of FBF and FVR for each point in each subject was the mean of the values obtained at each of those time points during the three tilts. Similarly, we averaged the two values for 15, 30 and 45 s after application of the cold face stimulus.

**Statistical methods**

Results are expressed as mean values ± standard error of the mean. We tested the linear relation between variables using Pearson’s correlation coefficient and least squares linear regression analysis. We assessed simultaneous independent effects of continuous variables by multivariate linear regression. For the tilt and cold face stimulus data, we performed statistical analysis using the general linear models procedure (to allow for differing group sizes) for repeated measures ANOVA, with group and time point as factors. We also studied summary statistics (maximum changes in SBP, DBP, heart rate, FBF and FVR, and time to maximum change) and differences between groups using Student’s unpaired two-tailed t test (after confirmation of normality using the Shapiro–Francia W test). A P value of < 0.05 was regarded as statistically significant.

**Results**

**Clinic blood pressure**

The mean clinic supine SBP for the whole group was 172 ± 7 mmHg and mean DBP 91 ± 3 mmHg. The equivalent standing values were 168 ± 6/98 ± 3 mmHg. Mean values for the hypertensive and normotensive groups are shown in Table 1.

The mean change in clinic SBP on standing was 5 ± 2 mmHg, range −14 (the negative sign representing a rise in blood pressure on standing) to 37 mmHg (asymptomatic). Postural blood pressure change was greater in those with higher initial SBP ($r = 0.67$, $P < 0.001$), such that the blood pressure fall with active standing was greater in the hypertensive group than in the normotensive group (8 ± 3 mmHg versus −2 ± 2 mmHg; $P = 0.012$).

**Laboratory cardiovascular tests**

Values for BRS from the Valsalva manoeuvre and the pharmacological pressor and depressor methods are given in Table 1. All three methods gave significantly lower values for BRS in the hypertensive group.

The blood pressure, heart rate, FBF and FVR responses to 60° head-up tilt are shown in Table 2. Baseline FBF and FVR did not differ between the two groups, and neither did the changes in these measures evoked by tilting. Figure 1a shows the whole FVR response to passive tilt in the two groups (effect of time, $F = 1.66$, $P = 0.13$; effect of group, $F = 0.16$, $P = 0.69$). Systolic and diastolic blood pressure fell more
with tilt in the hypertensive subjects, and the nadir was usually at a later point after tilting (Table 2). The hypertensive group also showed a reduced heart rate increment with tilt compared with normotensive subjects.

The responses to the non-baroreceptor-mediated cold face stimulus are shown in Table 3. The systolic and diastolic blood pressure responses were significantly greater in the hypertensive subjects and occurred later. Once again, the two groups showed no difference in baseline FBF and FVR or in the change in FBF in response to the stimulus, but the maximum increase in FVR on stimulation was larger in the hypertensive subjects. There was also a significant difference between the two groups when we examined the entire response (Figure 1b; effect of time, $F = 1.11$, $P = 0.35$; effect of group, $F = 3.80$, $P < 0.05$). There were no within-subject differences in baseline FBF and FVR between the tilt and the cold face stimulus studies.

### Orthostatic responses and BRS

Blood pressure changes in response to active standing in the clinic and in response to $60^\circ$ head-up tilt in the laboratory were significantly correlated ($r = 0.73$, $P < 0.001$), although the absolute values seen with passive tilting were much greater ($P < 0.0001$). The relations between postural blood pressure change and BRS are shown in Figure 2 and Table 4 (before and after adjustment for the confounding effect of baseline SBP).

With all three methods of baroreflex assessment—irrespective of the pressor or depressor nature of the baroreflex stimulus—there is a consistent inverse association between BRS and the fall in blood pressure with postural change. The blood pressure fall with orthostasis was also correlated with increasing age ($r = 0.58$), but this was not independent of simultaneous changes in BRS and SBP.

The fall in blood pressure with both active standing and passive tilt was strongly correlated with the prevailing level of SBP ($\Delta$SBP standing, $r = 0.67$, $P < 0.001$; $\Delta$SBP tilt, $r = 0.60$, $P = 0.001$). With the use of simultaneous multivariate analysis to adjust for the potential confounding effect of baseline SBP, the fall in blood pressure with tilt was independently related to BRS at any given level of SBP (Table 4). The exception was the sodium nitroprusside-based BRS, which was not related to orthostatic blood pressure change independent of the level of SBP.

### Discussion

Our observation of a relationship between increasing supine blood pressure and greater falls in blood pressure with orthostasis in elderly people confirms the conclusions of several other studies [3, 4, 6] and suggests a pathophysiological explanation. Our data confirm the findings from previous studies that
impairment of cardiovascular reflexes (whether with hypertension or ageing) produces inadequate homeostatic responses to environmental influences such as food [20] or changing posture. Greater blood pressure falls with passive tilt were strongly associated with impaired arterial BRS, and intact sympathetic efferent function (as judged from the blood pressure and vascular resistance response to a non-baroreflex-mediated sympathetic stress, such as the cold face stimulus) was insufficient to counteract the blood pressure fall. Indeed, the observation of important falls in blood pressure with tilt in normotensive subjects would suggest that, irrespective of hypertension-related vascular structural changes in the resistance vasculature [21], a 50% fall in FBF may be the maximum achievable response even in normotensive elderly people. Thus it may be the further impairment of the cardiac baroreflex that is responsible for the greater blood pressure falls seen in hypertensive subjects.

The absolute blood pressure changes in both groups were greater than those described [22], probably due to the use of the continuous Finapres method for recording blood pressure, rather than an intermittent method [23]. The continuous method ensured the capture of the nadir of blood pressure, whenever it occurred. No patient reported dizziness or faintness during tilting. Vardan et al. [24], who used intra-arterial blood pressure monitoring, also found much larger falls in SBP in elderly people on passive tilting than are usually found with intermittent recordings.

The relationship between high baseline SBP and greater changes in blood pressure with tilt is an example of the association between the magnitude of a change and its initial value (regression to the mean). This effect can be minimized by repeated measurements of blood pressure and by the use of multiple regression analysis to adjust for the confounding effect of the related variable (in this case, baseline SBP). Although we cannot entirely exclude an effect of this phenomenon in this study, our results from multiple regression analysis support the contention that the impairments of cardiovascular homeostasis seen with hypertension may also be responsible for the associated orthostatic hypotension, with baroreflex sensitivity being related to orthostatic blood pressure change after adjustment for the prevailing level of SBP. Although BRS values derived from the Valsalva method and the phenylephrine method were independently related to orthostatic blood pressure change, these methods assess BRS from the bradycardic response to a rise in SBP, and the method based on the tachycardic response to a fall in SBP (the nitroprusside method) did not demonstrate an independent association. We have previously shown that all three methods of BRS measurement are highly correlated [14, 21], so this latter observation may represent a type II statistical error in our relatively small study group.

This is the first study to compare orthostatic blood pressure changes and direct measurement of arterial baroreceptor–heart rate reflexes in otherwise healthy and asymptomatic elderly people with a wide range of blood pressures (including subjects with or without hypertension). Johnson and colleagues [25] described an association between orthostatic hypotension and impaired blood pressure responses to the Valsalva manoeuvre in institutionalized elderly patients. Robinson and colleagues [10] reported no differences in the heart rate response to tilting between frail elderly subjects with or without orthostatic hypotension but with similar levels of SBP. White [7] demonstrated a smaller and slower rise in heart rate in elderly subjects with orthostatic hypotension. Rowlands et al. [9] studied the responses to both tilt and phenylephrine injection in elderly hypertensive and normotensive subjects and found greater falls in SBP after prolonged tilt in the hypertensive group; no attempt was made to relate BRS to the response to orthostatic stress.

In young patients with symptomatic orthostatic
### Table 3. Blood pressure, heart rate, forearm blood flow and forearm vascular resistance responses to the cold face stimulus for the hypertensive and normotensive groups

<table>
<thead>
<tr>
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<th>Hypertensive</th>
<th>Normotensive</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
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<tr>
<td>Maximum increase (mmHg)</td>
<td>27 ± 4</td>
<td>14 ± 2</td>
<td>0.01</td>
</tr>
<tr>
<td>Time to peak (s)</td>
<td>26 ± 4</td>
<td>14 ± 5</td>
<td>0.06</td>
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<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td></td>
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<tr>
<td>Maximum increase (mmHg)</td>
<td>11 ± 3</td>
<td>5 ± 1</td>
<td>0.05</td>
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<tr>
<td>Time to peak (s)</td>
<td>32 ± 3</td>
<td>18 ± 5</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Maximum increase (bpm)</td>
<td>5 ± 2</td>
<td>1 ± 1</td>
<td>0.04</td>
</tr>
<tr>
<td>Time to peak (s)</td>
<td>36 ± 4</td>
<td>23 ± 6</td>
<td>0.08</td>
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<tr>
<td><strong>Forearm blood flow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (ml.min⁻¹.100 ml⁻¹)</td>
<td>2.7 ± 0.4</td>
<td>2.1 ± 0.3</td>
<td>0.29</td>
</tr>
<tr>
<td>Maximum reduction (%)</td>
<td>25 ± 5</td>
<td>20 ± 3</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Forearm vascular resistance</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline (units)</td>
<td>58 ± 8</td>
<td>52 ± 6</td>
<td>0.56</td>
</tr>
<tr>
<td>Maximum increase (units)</td>
<td>29 ± 7</td>
<td>13 ± 3</td>
<td>0.05</td>
</tr>
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</table>

**Figure 2.** Relation between maximum change in systolic blood pressure (SBP) with passive tilt and arterial baroreceptor–cardiac reflex sensitivity assessed by responses to the Valsalva manoeuvre, phenylephrine injection or sodium nitroprusside infusion in hypertensive (▲) and normotensive (●) subjects. ---, line of regression.
hypotension, El-Sayed and Hainsworth [8] found that a reduced tolerance to orthostatic stress was related to increased (rather than decreased) carotid BRS (using the neck suction method). They suggested that a baroreflex sensitivity of less than 10 ms/mmHg was effective protection against orthostatic intolerance. It is difficult to translate the possible implications of their study of otherwise healthy young subjects with unexplained syncopal episodes to a group of asymptomatic elderly subjects—particularly as most subjects in our study had baroreflex sensitivities of less than 10 ms/mmHg. Indeed, our data suggest the opposite relationship: that the orthostatic hypotension seen with hypertension is independently associated with reduced BRS.

The results of our study differ from those of Tonkin and colleagues [11, 26] of elderly subjects with either normal blood pressure or isolated systolic hypertension [26]. They found no differences in blood pressure or heart rate responses to 60° tilt, the cold pressor test or isometric exercise between the groups. However, their technique of measuring blood pressure only at the end of 10 min of tilt would not have detected potentially important changes early during tilt: in our study, the nadir of SBP occurred within 1-2 min of tilting. They found that the hypertensive subjects had a larger increment in FVR than normotensive subjects to cold stress, but not to tilt. While this is in agreement with our results, they concluded [26] that there was no difference in cardiovascular reflex behaviour with systolic hypertension beyond that due to age and that there was thus no evidence for a causative association between high blood pressure and orthostatic hypotension. Yo et al. [27] studied the responses to tilt examined by spectral analysis of heart rate variability and found no difference in the changes in parasympathetic activity or sympattho-vagal balance between older subjects with or without hypertension. However, this was despite a much greater fall in blood pressure in the hypertensive subjects, again questioning the adequacy of these sympathetic responses with larger orthostatic blood pressure changes.

Our study has some limitations. First, we did not include subjects with symptomatic orthostatic hypotension, although several subjects had blood pressure falls with tilt to a level often associated with symptoms. Care is needed in generalizing our findings to subjects with orthostatic symptoms or those with greater degrees of postural hypotension. We did not measure sympathetic responses to tilt from either venous catecholamines or from microneurographic studies [28]. The problems of inferring alterations in sympathetic function from venous plasma catecholamines are recognized [29]. However, Rowlands et al. [9] did not find any greater rise in plasma noradrenaline with tilt in elderly hypertensive subjects than in normotensives and Lye et al. [30] found that the increment in plasma noradrenaline with tilt was unrelated to the postural blood pressure change. Our assessment of the baroreflex-mediated cardiac response to orthostasis provides no data about the specific location within the reflex of any dysfunction [6]. We confined our study to changes in heart rate, without measurement of other baroreflex-related changes—particularly in stroke volume (although the two are closely related [31]). The stroke volume changes with orthostasis may be influenced by baroreflex-mediated vasoconstriction. This also contributes to the adaptive response to postural change but was not assessed by us. The contribution of this side of the reflex is implied by the relationship between orthostatic hypotension and varicose veins [1]. We made no attempt to distinguish between the responses to orthostasis of low-pressure cardiopulmonary reflexes and high-pressure arterial baroreflexes. The response to tilt is complex, invoking stimulation of both systems, but the test does not distinguish between them. Non-hypotensive lower-body negative pressure and passive leg raising can stimulate and inhibit cardiopulmonary receptors
Baroreflexes and orthostasis

exclusively. These responses would be of interest given the impairment of these reflexes with ageing and hypertension. Finally, measuring baroreflex-mediated vasoconstriction through changes in the forearm vasculature may have underestimated the response, as—at least in younger subjects—vasoconstriction of the viscera is more important in the orthostatic response [32].

Clinical decisions on the treatment of hypertension in elderly people are often influenced by a fall in blood pressure on standing. Although this implies that such a fall will be exacerbated by drugs, this may not be so. In the treatment of isolated systolic hypertension, the Systolic Hypertension in the Elderly Program [33] reported no increased incidence of symptoms related to orthostatic intolerance or falls in the diuretic-based treatment group. Elderly subjects with isolated systolic hypertension treated with modified-release dihydropyridine calcium-channel blockade show improvements in orthostatic tolerance and other aspects of cardiovascular homeostasis [34]. We must not deny elderly hypertensive patients effective stroke prevention simply because of a perception that it will inevitably provoke or exacerbate postural symptoms or orthostatic hypotension in them.

In conclusion, we have shown that orthostatic blood pressure changes assessed either by active standing or passive tilting are greater in elderly subjects with higher SBP. Hypertensive subjects display apparently maximal forearm vasoconstriction but an inadequate baroreflex response, leading to greater falls in blood pressure with passive tilt. The fall in blood pressure with orthostasis is associated with decreased arterial baroreflex sensitivity after adjustment for baseline blood pressure. This suggests a pathophysiological link between the disordered cardiovascular homeostasis that characterizes the hypertensive condition and the orthostatic hypotension that often accompanies it.

Key points

- Hypertension is often accompanied by orthostatic hypotension and this may influence decisions on antihypertensive treatment of elderly subjects.
- Hypertensive subjects have a greater fall in systolic blood pressure with active standing and passive tilt than normotensive subjects despite greater nonbaroreflex-mediated responses to sympathetic stress.
- Hypertensive subjects have a reduced baroreceptor–heart rate reflex sensitivity related to the orthostatic change in blood pressure—even after adjustment for the confounding effect of baseline systolic blood pressure.
- One factor responsible for the observed association between supine hypertension and orthostatic hypotension may be impaired baroreceptor–heart rate reflex sensitivity.

References

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