Initial orthostatic hypotension: review of a forgotten condition

Wouter WIELING*, C. T. Paul KREDIET*, Nynke VAN DIJK†, Mark LINZER‡ and Michael E. TSCHAKOVSKY§

*Department of Internal Medicine, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, †Clinical Epidemiology and Biostatistics (NvD), Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, ‡Department of Medicine, University of Wisconsin, Madison, Wisconsin, U.S.A., and §School of Physical and Health Education, Queen’s University, Kingston, Ontario, Canada

ABSTRACT

Several studies have shown that standing up is a frequent (3–10%) trigger of loss of consciousness both in young and old subjects. An exaggerated transient BP (blood pressure) fall upon standing is the underlying cause. IOH (initial orthostatic hypotension) is defined as a transient BP decrease within 15 s after standing, >40 mmHg SBP (systolic BP) and/or >20 mmHg DBP (diastolic BP) with symptoms of cerebral hypoperfusion. It differs distinctly from typical orthostatic hypotension (i.e. BP decrease >20 mmHg SBP and/or >10 mmHg DBP after 3 min of standing) as the BP decrease is transient. Only continuous beat-to-beat BP measurement during an active standing-up manoeuvre can document this condition. As IOH is only associated with active rising, passive tilting is of no diagnostic value. The pathophysiology of IOH is thought to be a temporal mismatch between cardiac output and vascular resistance. The marked decrease of vascular resistance during rising is similar to that observed at the onset of leg exercise and is absent during head-up tilting. It is attributed to vasodilatation in the working muscle through local mechanisms. Standing up causes an initial increase in venous return through the effects of contraction of leg and abdominal muscles. The consequent sudden increase in right atrial pressure may contribute to the fall in systemic vascular resistance through a reflex effect. This review alerts clinicians and clinician scientists to a common, yet often neglected, condition that occurs only upon an active change of posture and discusses its epidemiology, pathophysiology and management.

INTRODUCTION

In 1927, Bjure and Laurell [1] described patients with complaints of almost immediate light-headedness, blurred vision on rising, postural tachycardia and impaired orthostatic tolerance upon standing. The condition was postulated to be common in young asthenic subjects and was attributed to increased pooling of venous blood in the presence of intact autonomic regulatory mechanisms [1,2]. Without an apparent connection, in the same year, the famous German physiologist Hering also wrote about the condition [3]. However, the earliest clinical report dates back to 1864, when Liebermeister [4] described three subjects (a 50-year-old man, a 40-year-old woman and a male medical student) with syncopal episodes shortly after rising from prolonged recumbence. In 1932, Sir Thomas Lewis also referred to IOH (initial orthostatic hypotension) in his classical lecture on vasovagal syncope, writing “There is another and frequent form of giddiness occasionally leading up to syncope, which is due to a distinct mechanism; it is characteristic of this giddiness that it is usually related to the act of rising to the erect position” [5].

Over the last few decades, various groups have reported that IOH is a frequent cause of orthostatic complaints and special tests were designed to test for it [6–15]. The
introduction of finger volume photoplethysmography BP (blood pressure) monitoring (i.e. Finapres) in the 1980s, with its ability to measure the arterial pressure non-invasively and continuously, allowed for the objective assessment of patients with complaints of IOH [9–11, 13–19]. This led to an ongoing research effort into the mechanism underlying this condition in our department [20–24].

Without continuous BP monitoring, the documentation of patients presumed to suffer from IOH is problematic, as the rapid changes in arterial BP involved cannot be assessed with routine conventional BP equipment (Figures 1 and 2) [7,9,11,13,17]. Perhaps for that reason, previous reviews dealing with (near)syncope discuss orthostatic hypotension, but do not distinguish initial from late [25–28]. The aim of this review is to alert clinicians and clinician scientists to a fairly common, yet often neglected, condition that occurs only upon an active change of posture and to discuss its epidemiology, pathophysiology and management.

**EPIDEMIOLOGY**

Many people are familiar with the occasional experience of a brief feeling of light-headedness and sometimes visual complaints, such as seeing black spots, almost immediately following standing up. These symptoms are characterized by their time of onset (5–10 s after standing up) and short duration (disappearance of symptoms within 20–30 s) (Figures 1 and 2) [17]. The complaints occur especially after prolonged supine rest [3,29] or after arising from the squatting position [30,31].

In teenagers and adolescents, fainting upon standing appears to be fairly common in the general population [32]. De Maréès [7] reported that 22 % of Hanover students (n = 466) "often or always had complaints of seeing black spots immediately after rising" and our group [33] has found that 8 % of medical students, who had experienced one or more episodes of transient loss of consciousness, related it to standing up. As there is no readily apparent alternative diagnosis, it may be reasonable to assume that in the majority of these patients an exaggerated fall in BP upon standing was the underlying cause.

The incidence of IOH as a cause of syncope in the general population is unknown. In the recent Fainting Assessment Study [34], the history of 503 consecutive patients with transient loss of consciousness who presented to the Academic Medical Center of the University of Amsterdam (mean age, 52 ± 19; 56 % males) was systematically taken by means of a standardized questionnaire. Details on this study have been described elsewhere [34]. In this study, IOH as a primary diagnosis had an incidence of 3.6 %, which is higher than other forms of
Initial orthostatic hypotension: review of a forgotten condition

Figure 2 Continuous BP monitoring during active standing (left) and during head-up tilting (right) in 11 healthy volunteers
The thick and thin lines represent intra-arterial measurement and Finapres measurement respectively. Note the striking difference between the two initial responses to orthostatic stress. IOH can only be documented during an active standing manoeuvre. Reprinted from Cardiovascular Research, 24, Imholz, B.P., Settels, J.J., van der Meiracker, A.H., Wesseling, K.H. and Wieling, W., (1990) Non-invasive continuous finger blood pressure measurement during orthostatic stress compared to intra-arterial pressure, pp. 214–221, © (1990), with permission from the European Society of Cardiology.

Figure 3 Haemodynamic responses to standing up and tilting in eight healthy subjects
Vertical lines indicate start of the manoeuvres. MABP, mean BP; SV (stroke volume), CO (cardiac output) and TPR (total peripheral resistance) were determined by Modelflow [97]. Standing up induces a fall in BP and a rise in CO. Consequently, TPR falls to 40% below control levels. This contrasts with gradual circulatory changes after tilt. Reproduced from [22] and used with permission. © (1991) American Physiological Society.

situational syncope, i.e. micturition syncope (2.6%), defecation syncope (0.4%) and cough syncope (1.6%) (these latter incidences are similar to those reported previously [35,36]). A total of 17% of patients reported standing up as one of the primary triggers for loss of consciousness, and 37% of all patients were familiar with light-headedness in response to standing up.

POSSIBLE MECHANISMS UNDERLYING THE INITIAL FALL OF ARTERIAL BP UPON STANDING

Complaints of light-headedness and even fainting upon active standing are related to a marked transient fall in arterial BP that also occurs in healthy subjects upon active standing (Figures 1 and 2) [22,37,38]. Comparable events are observed on arising from sitting [18,24,31,39,40] or squatting [30,31] and at the onset of whole-body exercise without a change in posture, such as the bicycle exercise (Figures 2–5) [24,40]. This initial BP response to the upright position is exclusively associated with active rising. In passive tilting, any fall in pressure is much smaller and in most cases absent (Figures 1–3) [22–24,37,38,41,42]. Thus a prerequisite for the observed hypotension appears to be muscle contraction.

Arterial BP reflects a balance between the rate of blood volume entering and leaving the arterial vasculature (cardiac output and peripheral resistance effects respectively). Thus initial hypotension upon standing indicates that the rate at which blood volume is entering the arterial circulation is temporarily less than the rate leaving (i.e. cardiac output is not matching peripheral resistance effects on arterial outflow). As it has been established
that this mismatch is due to a reduction in peripheral resistance [22,40,43] and not cardiac output, and since the observed hypotension requires muscle contraction, three potential mechanisms have been proposed: (i) the muscle pump, (ii) rapid locally mediated vasodilatation effects (both factors in the active muscles involved in the effort of standing up), and (iii) cardiopulmonary-receptor-mediated systemic sympathetic withdrawal in response to sudden increases in right atrial pressure. Before these mechanisms are considered, a description of the haemodynamic changes that occur on active standing is provided.

**Initial haemodynamic response to active standing**

There is an immediate increase in HR (heart rate) upon standing, which peaks at approx. 3 s (Figure 3). This results from abrupt inhibition of cardiac vagal activity (it is absent after parasympathetic blockade) [38,41,44,45]. This vagal inhibition has been attributed to a general exercise reflex activated by two mechanisms. One is 'central command', related to the motor signals from higher brain centres that stimulate the brainstem cardiovascular centres [46,47], and the other is a feedback reflex from the contracting muscles due to activation of their mechanoreceptors (muscle–heart reflex) [48]. At the same time, stroke volume remains stable (Figure 3). This is probably due to an elevation in right atrial pressure which compensates for reduced diastolic filling time as HR is increased.

The combination of the instantaneous and substantial HR increase and stable stroke volume results in a pronounced increase in cardiac output, with a maximum approx. 7 s after the onset of standing up (Figure 3) [19,22]. Nevertheless, a simultaneous fall of approx. 25 mmHg in mean arterial BP is found [19,22,23] (Figure 3). This can only be explained by a pronounced fall in systemic vascular resistance, which some studies have shown to be approx. 40% [19,22,43]. In fact, there appears to be a strong relationship between the decrease in systemic vascular resistance and the depth of the BP trough [19].

A more gradual secondary HR increase towards a secondary peak at approx. 12 s after the onset of standing (Figure 3) results from the dual effects of further reflex
inhibition of cardiac vagal activity and an increase in sympathetic outflow to the heart [37,38,44]. The latter probably reflects arterial baroreflex compensation for the initial transient fall in arterial pressure (Figures 2 and 3). However, cardiac output has already returned to baseline when the HR peaks. This is due to a reduction in stroke volume resulting from a return of right atrial pressure to baseline (Figures 3 and 4). The rebound of arterial pressure, beginning after approx. 7 s (Figure 3), is the result of sympathetic vasoconstriction in the peripheral vasculature. We attribute this vasoconstriction to a combination of arterial hypotension-induced unloading of arterial baroreceptors and reduced venous return-induced unloading of cardiopulmonary mechanoreceptors [37,38]. The subsequent rapid decrease in HR at approx. 20 s is associated with a normalized, and in some instances, overshoot of arterial pressure, causing rapid vagal inhibition of the sinus node. Within 30 s after the initial disturbance, circulatory stabilization is reached (Figures 1 and 2).

Can the muscle pump explain transient hypotension with active standing? Leg and abdominal muscle contraction can empty venous vessels such that, upon muscle relaxation, the local arterial–venous pressure gradient difference is widened (for discussion on this subject, see [49]). This would be expected to elevate local blood flow. Systemically this would be an increase in arterial outflow and result in a fall in calculated peripheral resistance. Because it is not a true change in resistance, but rather due to the energy imparted by the muscle pump, it is termed a ‘virtual resistance’.

It has been argued previously [50] that this is the only mechanism capable of increasing muscle blood flow in the first few seconds of exercise. However, this elevation in flow would be maximal at the moment the muscles used in standing relax and then dissipate as the veins quickly refill. This does not correspond precisely with the time course of hypotension following a single muscular contraction caused immediate substantial increase in right atrial pressure (Figure 3), and its role remains to be confirmed.

Can rapid vasodilatation explain transient hypotension with active standing? Early work by Corcondilas et al. [51] indicated that a brief muscle contraction caused immediate substantial increases in flow, even when muscle venous pressure has returned to baseline, indicating rapid vasodilatation. Recently, evidence from in vivo human studies [52,53], isolated dog muscle [54] and intra-vital video microscopy examination of rodent muscle [55,56] have confirmed that resistance vessels in muscles dilate immediately and in proportion to muscle contraction intensity, and that local mechanisms are responsible. This vasodilatation peaks approx. 4 s after release of a brief contraction and then returns to normal over the next 10–20 s. As with the muscle pump, the role of rapid muscle vasodilatation remains to be confirmed.

Can the cardiopulmonary receptor reflex explain transient hypotension with active standing? The muscular effort of standing compresses the venous vessels in the contracting muscles of the legs (muscle pump) [39,57–60] and also increases intra-abdominal pressure (abdominal compression reflex) [61,62]. The increase in intra-abdominal pressure induced by standing up is pronounced. In a study in seven healthy subjects [19], an increase of 43 ± 22 mmHg was documented. The mechanical effects of the leg and abdominal compression are responsible for a sudden rise in right atrial pressure of 10–15 mmHg (Figure 4) via translocation of blood from the respective venous beds towards the heart. We have advanced the hypothesis that this immediate and substantial increase in right atrial pressure (Figure 4) activates cardiopulmonary mechanoreceptors initiating an abrupt reflex withdrawal of sympathetic vasoconstrictor tone, and a subsequent fall in total systemic vascular resistance lasting for 6–8 s [22,40,43].

It may be argued that a fall in systemic vascular resistance of approx. 40 % is surprisingly large, but so is the 10–15 mmHg abrupt rise in atrial pressure as a stimulus (Figure 4). In fact in a study by Vissing et al. [63], a gradual rise of on average 4 mmHg in right atrial pressure resulted in a 20 % fall in forearm vascular resistance and a 26 % fall in calf vascular resistance. Moreover, studies in patients with cardiac pacemakers suggest that a sudden increase in atrial pressure can induce severe hypotension [64].

Arguments against this hypothesis stem from observations by Sheriff et al. [50], where immediate hypotension at the onset of exercise in dogs occurred in control and sympathetic-blockade conditions, and because it is thought that the response speed of the sympathetic nervous system is too slow to explain the time frame of the observed hypotension [65,66]. However, other observations are in favour of it in that a reduction in sympathetic nerve activity has been shown during the first minute of leg exercise [67,68]. Re-infusion of pooled venous blood appears to be involved, since the reduction in muscle sympathetic activity is more pronounced in the upright than in the supine position.

Active standing from a squat evokes more severe transient hypotension Another observation that must be taken into consideration when searching for an explanation of IOH is that rising from squatting results in a deeper BP trough compared with standing up from supine (Figure 5) [6,30,31,69–71]. On average, BP in healthy young adults falls by 60 mmHg SBP (systolic BP) and 40 mmHg DBP.
(diastolic BP) with a nadir approx. 7 s after rising [31,71]. Mild symptoms of transient light-headedness are often present [7]. Rising to erect from squatting is a recognized trigger for a faint in daily life [33].

It seems likely that the reason for the large BP fall after standing from a squat may be as follows. During squatting, the leg and buttock muscles are active and there is a restriction of blood flow due to elevated intramuscular pressure compression of the vasculature [70,72]. This combination of compression of blood vessels, leading to relative ischaemia and active muscle contraction, is likely to result in local vasodilatation of the leg and buttock muscle vasculature. Thus, upon standing and loss of compression of the legs, there would be an immediate reduction in leg vascular resistance due to already existing locally mediated vasodilatation [31,70–72]. In addition, the muscular effort involved in standing up from a squat position is considerable, and it has been demonstrated that rapid vasodilatory mechanisms act in proportion to contraction intensity [49]. This would be expected to cause further vasodilatation. It would therefore be expected that lower limb vasodilatation would be greater in standing up from a squat than from supine or sitting.

In addition, marked pooling of blood in the venous vessels in the legs and abdomen, which have been compressed in the squatting position [31,71,72], results in a decrease in venous return and thereby in cardiac output. The combination of the two factors results in a rapid translocation of a large amount of arterial blood from the chest to the distensible venous capacitance system below the diaphragm.

This can be compounded further by straining of the muscles of the thorax, during or shortly after rising, which mechanically impairs cardiac output, and hyperventilation which leads to hypocapnia and thereby to cerebral vasoconstriction. The combination of arising from squatting, straining and hyperventilation can induce fainting in almost anybody (i.e. fainting lark) [73,74].

Effects of age

Standing up in elderly subjects is commonly accompanied by straining and an instantaneous brief rise in BP, followed by a fall in pressure as in younger subjects [21,75,76]. The transient fall in systemic BP does not increase with age [42,76] and a transient fall of up to 40 mmHg SBP and 20 mmHg DBP in the first 5–15 s on standing (with a subsequent return to a normal orthostatic BP, i.e. no typical orthostatic hypotension) is considered normal [10,18,20]. Nevertheless complaints of initial orthostatic light-headedness appear to be more frequent in otherwise healthy young subjects, rather than in adult or elderly subjects. The explanation could be that, for a given fall in systemic BP, the fall in cerebral blood flow is larger in the young [77], for which the underlying mechanism remains to be elucidated.

SUBJECTS PRONE TO IOH

There are some groups that are especially at risk for IOH. The first group includes young patients with an asthenic habitus. Often those patients also have postural tachycardia and a tendency to faint during prolonged standing [1,13,78,79]. Whether additional mechanical factors, such as compression of the vena cava [80,81], during standing up play a role is unknown. A second group of patients prone to IOH includes those taking medication interfering with vasoconstrictor mechanisms, such as α-blockers or sympathetic outflow blocking agents [82,83], and psychiatric medication [17,84]. A third group are patients with carotid denervation, due to failing short-term BP control [85,86].

CLINICAL EVALUATION OF IOH

History taking is the most important tool for the diagnosis of IOH [17]. Patients with IOH typically complain of light-headedness and black-out starting 5–10 s after rising, typically after prolonged recumbence [4,29]. Patients have often walked some steps before (near) fainting occurs. Such an interval between the moment of rising and the onset of symptoms corresponds to the latency time between the onset of cerebral hypoperfusion and symptoms, which is approx. 6 s [87,88].

Mandatory for the diagnosis of IOH is the absence of typical orthostatic hypotension. Therefore BP after standing for 3 min should be normal (i.e. decrease SBP < 20 mmHg and/or DBP < 10 mmHg from supine [89]). Otherwise the clinician should focus on typical (i.e. not initial) orthostatic hypotension.

The diagnosis of IOH can only be confirmed by an active standing test with continuous BP monitoring. A positive test (reproduction of symptoms and an initial fall in finger BP > 40 mmHg SBP and/or > 20 mmHg DBP) is very specific. However, in our experience, many patients with a typical history will have a negative test, suggesting the test has low sensitivity. As IOH is exclusively associated with active standing up, tilt-table testing (i.e. passive head-up tilting) is not a helpful diagnostic provocation (Figures 1 and 2).

In the 1960–1970s, rising to erect from the squatting position was widely reported in the German literature to assess initial orthostatic adjustments [7,69]. The squat-stand test was more recently introduced in the English literature as an orthostatic stress test [31,90]. In our experience, this test is more sensitive and has a very good intra-patient reproducibility [30], and is therefore especially feasible for patient education and to test new interventions. Other advantages of this test are that it only takes 1–2 min of squatting before rising (compared with at least 5 min of supine rest). However, since squatting also causes pre-syncope in healthy volunteers, the specificity
of this test is probably lower than standing up from supine.

**THERAPY**

Syncope episodes can be embarrassing, cause injuries and have a profound impact on the quality of patients’ lives [91,92]. A clear explanation of the underlying mechanism and avoidance of the main trigger (rapid rise) are the principal treatment options.

Understanding the pathophysiology provides the rationale for advising patients to rise slowly from supine [93], especially at night, and possibly sitting at the edge of the bed first. Changing provoking medication regimens that interfere with rapid BP control, such as α-blockers [82,83], should be considered. If feasible, measures expanding circulating volume, such as salt supplementation, are likely to have a stabilizing effect on the circulation [94]. However, the effects of any of these interventions have never been documented systematically. A novel approach is training in BP raising manoeuvres. We have found lower body muscle tensing immediately after standing is a very effective way in patients with IOH to decrease the fall in pressure and symptoms [95]. This combats the cause of IOH directly by reducing the venous pooling capacity in the lower body and sustaining cardiac output. Apparently the maintenance of cardiac output fully compensates for the hypothesized vasodilatory effect induced by the rapid increase in right atrial pressure [96]. Another approach is that of immediately bending over to lower the head upon standing [97]. This combats the magnitude of cerebral hypotension by increasing the hydrostatic contribution to the cerebral BP and compressing the abdominal venous reservoir.

**CONCLUSIONS**

Since the first clinical recognition of IOH 150 years ago, the condition has been investigated in numerous studies. As a result, its epidemiology and especially its pathophysiology have been illuminated, as set out in this review. IOH is the most common cause of situational syncope, and history taking is the paramount diagnostic tool. Reproduction of IOH is only feasible after an active standing up manoeuvre, possibly from squatting. Therapy focuses on patient education.

**ACKNOWLEDGMENTS**

W.W. is the recipient of Netherlands Heart Foundation Grants #99-181 and #2003B156, and has received an unrestricted educational grant from Medtronic Europe. He is a member of the executive committee of the Taskforce on Syncope of the European Society for Cardiology. C.T.P.K. is the recipient of a Dr E. Dekker Stipend 2004 (physician before specialty training, T’007) from the Netherlands Heart Foundation. The support from the Netherlands Heart Foundation is gratefully acknowledged.

**REFERENCES**
