



Initial orthostatic hypotension among patients with unexplained syncope: An overlooked diagnosis?

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ABSTRACT

Background: Initial orthostatic hypotension (IOH) is a clinical syndrome of transient orthostatic hypotension that is defined as a drop in blood pressure of >40 mm Hg systolic and/or >20 mm Hg diastolic within 15 s after standing, accompanied by symptoms of cerebral hypoperfusion, but without sustained orthostatic hypotension (blood pressure decrease >20/10 mm Hg after 1–3 min of standing). As the etiology of syncope remains unknown in a large proportion of patients, we hypothesized that IOH is highly prevalent among patients with unexplained syncope.

Methods: We studied 250 consecutive outpatients with unexplained syncope that were evaluated in the syncope-unit of our tertiary referral hospital. We measured hemodynamic changes in response to active standing using a beat-to-beat blood pressure measurement device, first after lying supine for >5 min and then after squatting for 30 s.

Results: 11.2% of the patients were diagnosed with syncope due to IOH, with a mean fall in blood pressure of $47.4 \pm 12.5/29.0 \pm 10.7$ mm Hg within 15 s after standing up. Therefore, IOH was the second commonest cause of syncope in our cohort. 46.2% of the patients diagnosed with syncope due to IOH used antihypertensive drugs, mostly betablockers (41.6%) and/or tamsulosin (24.9%). The squatting-to-standing-test in addition to the lying-to-standing-test resulted in only 3 additional patients diagnosed with syncope due to IOH.

Conclusions: IOH is highly prevalent among patients with previously unexplained syncope. Therefore, beat-to-beat blood pressure measurement should be considered in patients with unexplained syncope.

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1. Introduction

Initial orthostatic hypotension (IOH) is a clinical syndrome of transient orthostatic hypotension that results in dizziness and/or syncope shortly after standing up actively, but not on passive tilting [1]. It is defined as a decrease in blood pressure of at least 40 mm Hg systolic and/or 20 mm Hg diastolic within 15 s after standing up, accompanied by symptoms of cerebral hypoperfusion, but in the absence of sustained orthostatic hypotension (blood pressure decrease >20/10 mm Hg after 1–3 min of standing) [2]. Diagnosing IOH can be difficult due to the rapid changes in blood pressure. Hence, it cannot be detected with an intermittent (upper arm) blood pressure measurement, but only with continuous measurement of blood pressure during active standing (example in Fig. 1). As a result, its exact prevalence is still unclear. Since the etiology of syncope remains unknown in up to 33% of the patients [3–7], we hypothesized that IOH might be an important cause of

syncope among patients with unexplained syncope. Therefore, we evaluated a cohort of 250 patients with previously unexplained syncope for the presence of IOH by measuring hemodynamic changes (using a beat-to-beat blood pressure measurement device) in response to standing up actively from the lying position. As the fall in blood pressure is generally larger in case of standing up from the squatting position than from the lying position [1], we hypothesized that the squatting-to-standing-test would be more sensitive to detect IOH. Therefore, we also evaluated hemodynamic changes in response to standing up from the squatting position.

2. Methods

2.1. Patients and protocol

We reviewed data from 250 consecutive outpatients who were analysed because of unexplained syncope in the multidisciplinary syncope unit of our tertiary referral hospital between September 2015 and May 2017. All patients were previously analysed in a secondary hospital or in the emergency department, but were referred to our syncope unit as those analyses did not lead to a definitive diagnosis, i.e. the cause of syncope remained unexplained. Analysis in such multidisciplinary syncope unit is highly recommended as it reduces hospitalization, costs, and presumably the number of misdiagnosis [8]. In our

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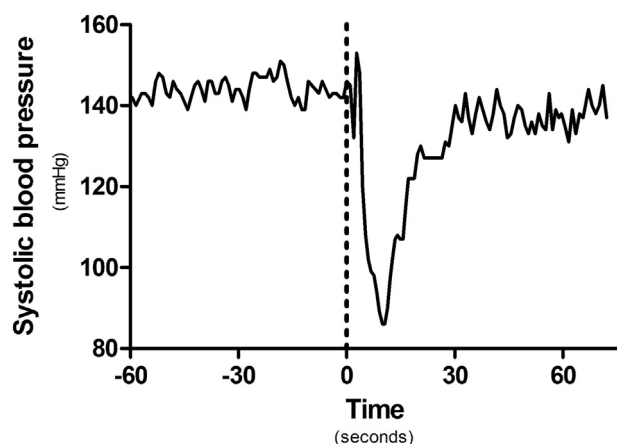


Fig. 1. Example of initial orthostatic hypotension. Beat-to-beat blood pressure measurement of a 60-year-old man standing up from the lying position (lying-to-standing-test), revealing initial orthostatic hypotension. Dotted line at $t = 0$ indicates time of standing up. Note the transient fall in blood pressure shortly after standing up, which was accompanied by a sensation of lightheadedness.

syncope unit, all patients were evaluated according to the same, standard clinical protocol. First, history was taken by two syncope experts (simultaneously): a cardiologist and either a neurologist or an internist/vascular medicine specialist. Subsequently, all patients underwent a standard diagnostic protocol, including electrocardiography, echocardiography, a beat-to-beat blood pressure measurement (see below), and laboratory testing (all on the same day). If considered clinically indicated additional tests were performed, such as long-term heart rhythm monitoring, cardiac exercise test, autonomic function tests (including Valsalva maneuver, deep breathing test, and carotid sinus massage), head-up tilt-table testing, electroencephalography, or additional imaging of the heart, brain, or vascular system. Thereafter, the diagnosis was established by consensus among the two syncope experts. In case of disagreement or doubt about the diagnosis, the case was reviewed by a multidisciplinary expert panel, consisting of (at least) one cardiologist, one neurologist, and one internist/vascular medicine specialist. Their consensus was decisive for the final diagnosis. The study was approved by the Medical Ethics Committee of the Maastricht University Medical Centre and complies with the Declaration of Helsinki. According to the Dutch law no written informed consent was needed because of the retrospective design of the study.

2.2. Measurements

We measured hemodynamic changes in response to active standing using a Nexfin device (BMEYE, Amsterdam, The Netherlands), a non-invasive, beat-to-beat blood pressure measurement device that measures arterial blood pressure continuously using the volume clamp method, reconstructs finger blood pressure to brachial blood pressure, and adjusts for vertical difference between the finger and heart based on height sensor. Reproducibility of these measurements (both under standardized and non-standardized conditions) has been evaluated previously [9–11]. The measurements were performed in a non-fasting state, between 1.00 and 4.30 p.m. in a quiet room maintained in a temperature of 21–23 °C. The finger cuff was applied around the middle finger of the right hand (size according to the manufacturer's instructions). The height sensor was placed on the chest at heart level and on the index finger of the right hand. Thereafter, baseline blood pressure recording was initiated while lying supine. Baseline blood pressure was verified with a digital upper arm blood pressure monitor (Omron M3, Omron Healthcare, Lake Forest, IL, USA) in order to detect measurement problems of the beat-to-beat blood pressure measurement device. In most cases, the finger cuff had to be replaced, but in case of other (unsolvable) measurement problems the patients were excluded from the present analysis. After at least 5 min of lying supine, the patients were instructed to stand up actively (in a timely manner) and stand still for 3 min (lying-to-standing-test). Thereafter, the patients were instructed to squat for 30–60 s (until blood pressure maintained stable) and then stand up (within 3 s) and stand still for 1 min (squatting-to-standing-test). During the whole test, beat-to-beat blood pressure was recorded. Shortly after standing up, the patient was asked whether symptoms of cerebral hypoperfusion had occurred (e.g. lightheadedness or dizziness).

2.3. Analyses

After the measurements we evaluated changes in blood pressure and heart rate upon active standing. As the beat-to-beat variation in blood pressure can be relatively large, we took the average blood pressure during the last 15 s before standing up as the baseline value. For the nadir of blood pressure within 15 s after standing up we took the average of 3 blood pressure values around the nadir. For the blood pressure after 1 and 3 min of standing the average during 15 s was taken.

Patients were diagnosed with syncope due to IOH if they met all of the following criteria:

- 1) Blood pressure criteria: Fall in blood pressure within 15 s after standing up of >40 mm Hg systolic and/or >20 mm Hg diastolic (measured at nadir).
- 2) Recognizable symptoms of hypoperfusion (e.g. light-headedness or dizziness).
- 3) No sustained orthostatic hypotension after 1 or 3 min (fall in blood pressure of >20 mm Hg systolic and/or 10 mm Hg diastolic).
- 4) History of syncope shortly after standing up (within 15 s), with IOH as the most likely clinical diagnosis (based on history taking by 2 syncope experts).
- 5) The absence of any clues for alternative diagnoses on additional diagnostic tests.

In case of any doubt on the diagnosis the case was reviewed by a multidisciplinary expert panel of at least 1 cardiologist, 1 neurologist, and 1 vascular-medicine specialist. The use of blood pressure lowering drugs was defined as the use of drugs that are known to lower blood pressure (beta-blockers, alpha-blockers, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, nitrates, or diuretics), irrespective whether it was prescribed for hypertension or for another indication (for example: alpha-blockers for lower urinary tract symptoms). We used SPSS (SPSS Inc., version 23.0, Chicago, Illinois, USA) for the statistical analyses. *t*-Tests (paired and unpaired) were used for continuous data (all normally distributed; expressed as mean \pm S.D.) and chi square test was used to assess categorical data. Correlation was tested using Pearson's R. A *p*-value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Out of 250 patients that were evaluated, 17 patients had to be excluded from the analyses of the beat-to-beat blood pressure data: 10 because of technical failure during the measurement, 2 because of data storage problems, 3 because of difficulties in evaluating the data due to heart rhythm abnormalities, and 2 because of the presence of a neurostimulator that interfered with the measurements. Therefore, beat-to-beat blood pressure data from 233 patients were available for analysis. Patient characteristics are summarized in Table 1. On average, patients were 61.7 ± 17.6 years old, with an average blood pressure of $132 \pm 22/76 \pm 11$ mm Hg (measured lying supine with a beat-to-beat blood pressure measurement device). 53.6% was female and 23.2% had a previous cardiovascular event.

3.2. Lying-to-standing-test

Out of 233 patients who underwent the lying-to-standing-test, 116 patients had a normal blood pressure response with an average fall in blood pressure within 15 s after standing of 11.7 ± 20.7 mm Hg systolic and 5.7 ± 12.7 mm Hg diastolic (Supplemental Fig. 1). 117 patients met the blood pressure criteria for IOH with a mean drop in blood pressure of 47.0 ± 14.4 mm Hg systolic and 29.3 ± 12.0 mm Hg diastolic within 15 s after standing up (Supplemental Fig. 1). However, as shown in Fig. 2a, 64 of these patients reported no recognizable symptoms of cerebral hypoperfusion during the test, 7 patients had sustained orthostatic hypotension, and in 23 patients an alternative diagnosis was considered more likely (alternative diagnoses are shown in Supplemental Table 1). Hence, 23 out of 233 patients were diagnosed with syncope due to IOH based on the lying-to-standing-test.

3.3. Squatting-to-standing-test

The squatting-to-standing-test was only performed in a subgroup 155 patients. The reason for this was that many patients had joint problems or were too frail to (safely) stand-up after squatting. Of these 155 patients, 127 met the blood pressure criteria for IOH with a mean fall in blood pressure of $49.4 \pm 17.6/35.4 \pm 13.1$ mm Hg within 15 s after standing up (Supplemental Fig. 2). However, as shown in Fig. 2b, 73 of these patients reported no recognizable symptoms of cerebral hypoperfusion during the test, 9 patients had sustained orthostatic hypotension, and in 35 patients an alternative diagnosis was considered more likely (Supplemental Table 1). Hence, only 10 out of 155 patients were diagnosed with syncope due to IOH after the squatting-to-standing-test. Of

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