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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 ± 12.5/29.0 ± 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.

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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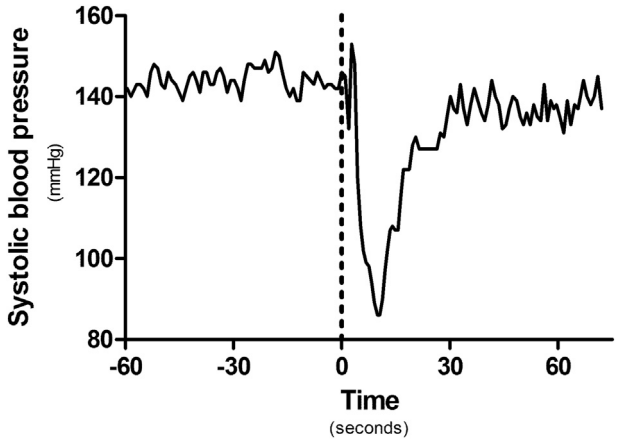

Fig. 1. Example of initial orthostatic hypotension. Beat-to-beat blood pressure measurement of a 60-year-old man standing up from the lying position (lying-to-standing-test), revealing initial orthostatic hypotension. Dotted line at $t = 0$ indicates time of standing up. Note the transient fall in blood 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 ± 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 ± 22/76 ± 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 ± 17.6/35.4 ± 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

Table 1
Characteristics of the patients.

Patient characteristic	n = 233
Female (n (%))	125 (53.6%)
Age (years)	61.7 ± 17.6
Body mass index (kg/m^2)	26.7 ± 4.4
Current smoking (n (%))	34 (14.6%)
Previous cardiovascular event (n (%))	54 (23.2%)
Previously diagnosed hypertension (n (%))	93 (39.9%)
Diabetes mellitus (n (%))	31 (13.3%)
Current use of blood pressure lowering drugs (n (%))	116 (49.8%)
Current us of antidepressants (n (%))	41 (17.6%)
eGFR (mL/min/1.73 m^2)	74 ± 23
Hemoglobin level (mmol/L)	8.6 ± 0.9
LDL (mmol/L)	2.9 ± 1.1
LVEF (%)	58.8 ± 6.7

Characteristics of the study patients. Values expressed as mean ± S.D. eGFR indicates estimated glomerular filtration rate using the CKD-EPI formula; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction.

these, 7 were already detected with the lying-to-standing-test. Therefore, the squatting-to-standing-test resulted in 3 extra diagnosis of IOH in addition to the lying-to-standing-test.

3.4. Patients with IOH

In total, 26 out of 233 patients (11.2%) were diagnosed with syncope due to IOH. Therefore, IOH was the second commonest cause of syncope in our cohort (Table 2). Mean fall in blood pressure among the patients diagnosed with syncope due to IOH was 47.4 ± 12.5/29.0 ± 10.7 mm Hg, with an increase in heart rate of 14.0 ± 15.6 beats per minute (Supplemental Fig. 3). Three of the 26 patients were diagnosed by the diastolic blood pressure fall only (i.e. drop in systolic blood pressure was <40 mm Hg, but drop in diastolic blood pressure was >20 mm Hg). Of the patients diagnosed with syncope due to IOH, 46.2% of the patients used antihypertensive drugs [mostly beta-blockers (41.6%) and/or tamsulosin (24.9%)] and 19.2% used antidepressant drugs. The use of these drugs by patients diagnosed with syncope due to IOH did not significantly differ from that by patients diagnosed with other causes of syncope. No differences were found between patients diagnosed with syncope due to IOH and the other patients with regard to age, gender, height, BMI, medical history, baseline blood pressure, or other patient characteristics (listed in Supplemental Table 2).

Eventually, the cause of syncope remained idiopathic in 26 patients (Table 2). Of those, 5 patients met the blood pressure criteria for IOH on the lying-to-standing-test and 8 on the squatting-to-standing-test. However, as history did not reveal that syncope was preceded by an active standing maneuver, the expert panel considered it unlikely that IOH was the cause of syncope in these patients. Hence, the cause of syncope in these patients was classified as idiopathic.

4. Discussion

In the present study we found that IOH is the second commonest cause of syncope (11.2%) among outpatients who were referred to our tertiary hospital because of previously unexplained syncope. Previous data on the prevalence of IOH among patients with syncope are scarce. In a study among 371 young adults (<30 years) with syncope, 7% was diagnosed with syncope due to IOH [12]. In that study, however, the diagnosis of IOH was based on history taking only. In a similar study among 503 patients with syncope, history taking alone pointed towards IOH in 3.6% of the cases [1,13]. Interestingly, the prevalence of IOH in our study was substantially higher. This may be caused by the fact that we studied a selected population of patients with unexplained syncope despite previous analysis in secondary hospitals or the emergency department. Furthermore, we measured hemodynamic changes upon standing in all patients, which inevitably increased awareness on initial orthostatic hypotension among doctors and patients.

Establishing the diagnosis of IOH is important for appropriate patient management. Volume expansion, sodium supplementation, interruption of interfering medication, instructions to stand up slowly, and counter maneuvers such as buttock clenching can improve quality of life and prevent recurrent syncope [1,12,14]. Moreover, it may reduce health care consumption as many patients are referred for additional diagnostic testing or second opinion as long as the cause of syncope remains unclear. The beat-to-beat blood pressure data could be used for patient education. In our experience, this can be very helpful for patients in understanding the cause of their symptoms and to demonstrate the efficacy of counter maneuvers. Unfortunately, beat-to-beat blood pressure measurement devices are not widely available yet, while intermittent (upper arm) blood pressure measurement is not able to detect the rapid changes in blood pressure that occur in IOH. In those settings IOH should still be considered as a working diagnosis in case of a typical clinical history.

In this study, we found that 50.2% of the patients met the blood pressure criteria for IOH, while IOH was considered the cause of syncope in "only" 11.2% of the patients. This large number of "false-positive" patients is to be expected, as a large population study demonstrated that IOH occurs in 32.9% of the population above 50 years old [15]. Interestingly, the presence of IOH in these relatively healthy subjects is not associated with an increased risk for syncope on the long term [16]. Therefore we would like to emphasize that history taking remains the cornerstone in the evaluation of unexplained syncope. Beat-to-beat blood pressure measurement can be a helpful diagnostic tool, but the diagnosis of IOH should only be made if history taking and other diagnostic tests point towards IOH as well. Conversely, natural intra-individual variation in blood pressure could lead to false-negative test-results [17], while IOH was present at the time of syncope for example due to volume depletion or a lower baseline blood pressure in the early morning. Therefore, in case of high clinical suspicion, repeated measurements should be considered to establish the diagnosis of IOH.

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. Given its limited additive value, one could consider reserving the squatting-to-standing-test for patients with high clinical suspicion for IOH, but with a negative lying-to-standing-test. However, one should keep in mind that the false-positive rate for the squatting-to-standing-test is even higher than for the lying-to-standing-test. This is presumably caused by the fact that the normal physiological drop in blood pressure during the squatting-to-standing-test is larger (on average 60 mm Hg systolic and 40 mm Hg diastolic in healthy individuals) as compared to that during the lying-to-standing test [1,18]. Therefore, it appears that the currently used cut-off for the squatting-to-standing test is not strict enough to accurately differentiate between IOH and a normal physiological response.

Given the high number of "false-positive" patients and the large number of healthy people meeting the blood pressure cut-off for IOH [15], the question arises whether a more stringent cut-off for IOH could improve its diagnostic value. Interestingly, a previous study among patients with Parkinson's disease suggested that the absolute nadir of blood pressure has a higher diagnostic value for detecting symptomatic orthostatic hypotension (thus with symptoms of cerebral hypoperfusion) than the change in blood pressure from baseline that is currently used [19]. Future studies among patients with symptomatic IOH as well as asymptomatic, age-matched controls are needed to evaluate whether this is also the case for IOH and whether the diagnostic criteria should be tightened.

In the present study, we were not able to point out clear risk factors for IOH. The use of blood pressure lowering drugs and antidepressants among patients with IOH was high, but comparable to that in patients without IOH. However, in our experience and according to previous literature, interrupting blood pressure lowering drugs (especially beta-

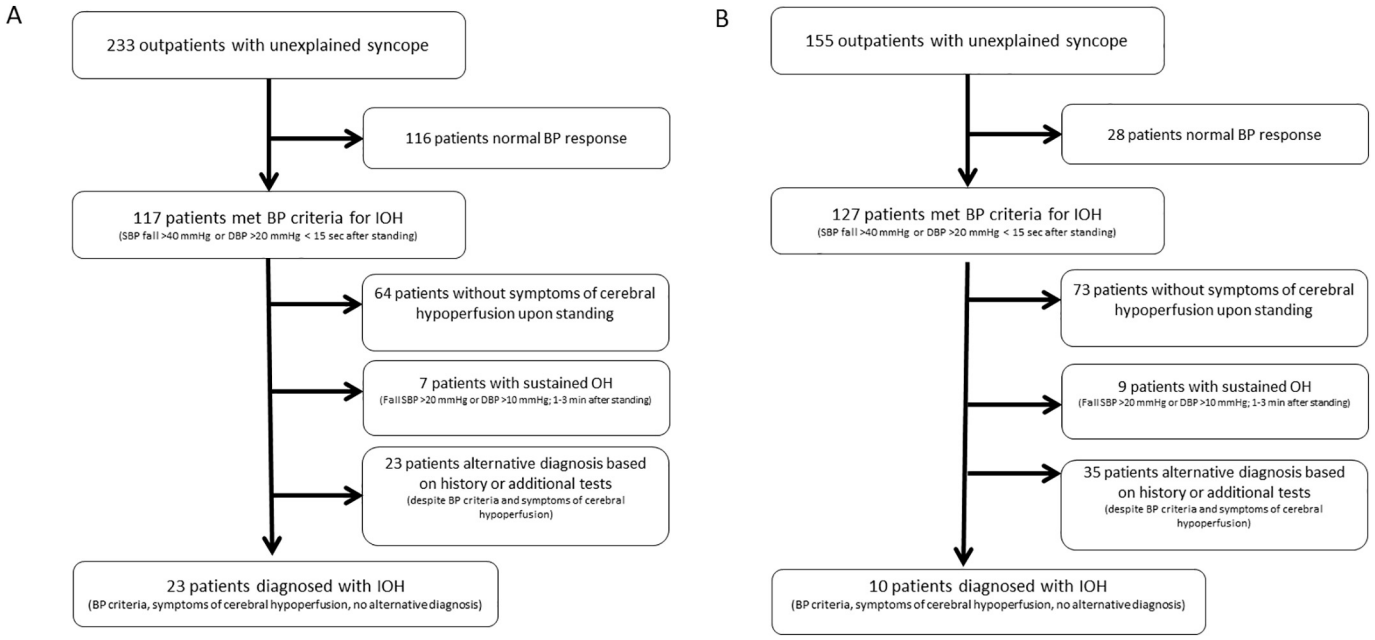

Fig. 2. A: Flow diagram of diagnosis of initial orthostatic hypotension using the lying-to-standing-test. BP indicates blood pressure; IOH, initial orthostatic hypotension; OH, orthostatic hypotension. B: Flow diagram of diagnosis of initial orthostatic hypotension using the squatting-to-standing-test. BP indicates blood pressure; IOH, initial orthostatic hypotension; OH, orthostatic hypotension.

blockers) [20] and antidepressants [21] could halt recurrent syncope in patients with IOH. The negative analysis in this study might be caused by the fact that we did not use an appropriate control group, but only a comparison with patients who were referred because of unexplained syncope with different etiology. These patients were relatively frail and often used blood pressure lowering drugs. Therefore we presume that the negative analysis in this study does not indicate that blood pressure lowering drugs do not contribute to the development of IOH, but merely that not all patients using blood pressure lowering drugs develop symptoms of IOH.

The present study is limited by the fact that we only performed a single measurement under semi-standardized conditions (in a clinical setting). As beat-to-beat blood pressure can vary over time [17], this may have led to under- or overdiagnosis of IOH, especially in cases were blood pressure was just above or below the cut-off. However, as history taking played a major role in establishing the diagnosis, the risk for overdiagnosis is considered to be small. Finally, this study was performed in a selected population of outpatients referred to a specialized syncope unit in a tertiary hospital. Therefore, the prevalence of IOH in this study cannot automatically be extrapolated to other clinical settings.

In conclusion, IOH is highly prevalent among outpatients with unexplained syncope referred to a tertiary hospitals syncope unit. Therefore, beat-to-beat blood pressure measurement during active standing should be considered in patients with unexplained syncope. However, as the false-positivity rate of such measurements is high, history taking remains the cornerstone in the evaluation of unexplained syncope. Future studies should evaluate whether different blood pressure cut-off points could improve the diagnostic value of these tests.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.05.043.

Table 2
Diagnosis after evaluation in a multidisciplinary syncope unit.

Diagnosis	n (%)
Reflex syncope	77 (33.0%)
Initial orthostatic hypotension	26 (11.2%)
Orthostatic hypotension	25 (10.7%)
Stumbling[a]	14 (6.0%)
Heart rhythm abnormality	13 (5.6%)
Autonomic dysfunction	7 (3.0%)
Psychogenic/hyperventilation	7 (3.0%)
Sleep disorder	7 (3.0%)
Vestibular dysfunction[a]	6 (2.6%)
Epilepsy[a]	5 (2.1%)
Other/multifactorial	18 (7.7%)
Idiopathic syncope	26 (11.2%)

Diagnosis in 233 outpatients with previously unexplained syncope after evaluation in a multidisciplinary syncope unit in a tertiary health care center.
[a] By definition, stumbling, vestibular dysfunction, and epilepsy are no syncope as no global cerebral hypoperfusion occurs.

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Disclosures/conflicts on interests

None.

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