Orthostatic Hypotensive Syncope: Diagnosis and Treatment

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Conflict of interest: none
**Classification**

- TLOC
  - Nontraumatic TLOC
    - Syncope
      - Reflex syncope
      - Orthostatic hypotension
      - Cardiac
  - Epileptic seizures
  - Psychogenic
    - Psychogenic pseudosyncope (PPS)
    - Psychogenic non-epileptic seizures (PNES)
  - Rare causes
    - Subclavian steal syndrome
    - Vertebrobasilar TIA
    - Subarachnoid haemorrhage
    - Cyanotic breath holding spell
Pure Autonomic Failure (PAF)
Definition

A Consensus definition of OH is a reduction of systolic blood pressure (SBP) of at least 20 mm Hg or diastolic blood pressure (DBP) of at least 10 mm Hg within 3 minutes of standing up. The use of a tilt table in the head-up position, at an angle of at least 60 degrees, was accepted as an alternative. OH may be symptomatic or asymptomatic. If the patient has symptoms suggestive of, but does not have documented OH, repeated measurements of BP should be performed. The values chosen are reasonable screening values but are associated with a 5% false positive. A value of 30 mm Hg fall in systolic blood pressure would reduce the frequency of false positives to 1%.

Update on Management of Neurogenic Orthostatic Hypotension

Phillip A. Low and Wolfgang Singer


SAP values less than 90 mmHg (*)
• A variant of OH is the *delayed OH*, which occurs after 3 minutes of standing; this might represent a mild form of sympathetic adrenergic dysfunction (Gibbons CH et al 2006)

• OH may occurs after 15 seconds of standing (*initial or transient OH*) (Wieling W et al 2007), possibly expression of transient mismatch between cardiac output and peripheral vascular resistance.
# Epidemiology - Frequency of the causes of syncope according to the settings

<table>
<thead>
<tr>
<th>Setting</th>
<th>Source</th>
<th>Reflex (%)</th>
<th>Orthostatic hypotension (%)</th>
<th>Cardiac (%)</th>
<th>Non syncopal T-LOCs (%)</th>
<th>Un-explained (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>Framingham studies</td>
<td>21</td>
<td>9.4</td>
<td>9.5</td>
<td>9</td>
<td>37</td>
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<tr>
<td>Emergency department</td>
<td>Ammirati</td>
<td>35</td>
<td>6</td>
<td>21</td>
<td>20</td>
<td>17</td>
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<tr>
<td></td>
<td>Sarasin</td>
<td>38</td>
<td>24</td>
<td>11</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Blanc</td>
<td>48</td>
<td>4</td>
<td>10</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Disertori</td>
<td>45</td>
<td>6</td>
<td>11</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Olde Nordkamp</td>
<td>39</td>
<td>5</td>
<td>5</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td></td>
<td><strong>35-48</strong></td>
<td><strong>4-24</strong></td>
<td><strong>5-21</strong></td>
<td><strong>8-20</strong></td>
<td><strong>17-33</strong></td>
</tr>
</tbody>
</table>
# Epidemiology - Frequency of the causes of syncope according to age

<table>
<thead>
<tr>
<th>Age</th>
<th>Source</th>
<th>Reflex (%)</th>
<th>Orthostatic hypotension (%)</th>
<th>Cardiac (%)</th>
<th>Non syncopal T-LOCs (%)</th>
<th>Unexplained (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>Olde Nordkamp</td>
<td>51</td>
<td>2.5</td>
<td>1.1</td>
<td>18</td>
<td>27</td>
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<tr>
<td>40-60 years</td>
<td>Olde Nordkamp</td>
<td>37</td>
<td>6</td>
<td>3</td>
<td>19</td>
<td>34</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>Del Rosso</td>
<td>68.5</td>
<td>0.5</td>
<td>12</td>
<td>-</td>
<td>19</td>
</tr>
<tr>
<td>&gt;60/65 years</td>
<td>Del Rosso</td>
<td>52</td>
<td>3</td>
<td>34</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Ungar</td>
<td>62</td>
<td>8</td>
<td>11</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Olde Nordkamp</td>
<td>25</td>
<td>8.5</td>
<td>13</td>
<td>12.5</td>
<td>41</td>
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<tr>
<td>&gt;75 years</td>
<td>Ungar</td>
<td>36</td>
<td>30</td>
<td>16</td>
<td>-</td>
<td>9</td>
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</tbody>
</table>

2018 ESC Guidelines on Syncope – Michele Brignole & Angel Moya
EHJ Doi:10.1093/eurheartj/ehy037

www.escardio.org/guidelines
Aging

- OH in 7% of normotensive aged individuals and in 30% of those with comorbidities

- Pathophysiology
  - reduced LV filling (LV diastolic dysfunction)
  - alterations in the mechanisms counteracting a reduction of the intravascular volume (↓ renine, aldosterone, angiotensin, vasopressin e sensazione di sete, ↑ atrial natriuretic peptide)
  - reduced baroreceptor sensitivity (↓ chronotropic and vascular α-adrenergic responses)
  - alterations in cerebro-vascular autoregulatory function
Orthostatic hypotension affects about 6% of subjects in the middle age and it is associated to an *increase of mortality and cardiovascular acute events* independently of the presence of other traditional risk factors.

(Fedorowski et al. European Heart Journal 2010; 31: 85-9)
Kaplan-Meier survival curves by OH status

Pathophysiology

Reflex Syncope

Inappropriate reflex

low BP/ cerebral hypoperfusion

low cardiac output

Cardiac Syncope

arrhythmia

structural cardiac

others

Hypovolemia

drug-induced auton. failure

primary auton. failure

structural damage ANS

secondary auton. failure

inadequate venous return

volume depletion

venous pooling

Orthostatic Hypotension

mixed

cardio-inhibitory

vaso-depressor

www.escardio.org/guidelines
Classification
Syncope due to orthostatic hypotension

- **Drug-induced OH (most common cause of OH):**
  - e.g. vasodilators, diuretics, phenothiazine, antidepressants,

- **Volume depletion:**
  - haemorrhage, diarrhoea, vomiting, etc.

- **Primary autonomic failure (neurogenic OH):**
  - pure autonomic failure, multiple system atrophy, Parkinson’s disease, dementia with Lewy bodies.

- **Secondary autonomic failure (neurogenic OH):**
  - diabetes, amyloidosis, spinal cord injuries, auto-immune autonomic neuropathy, paraneoplastic autonomic neuropathy, kidney failure.

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*Note. Hypotension may be exacerbated by venous pooling during exercise (exercise-induced), after meals (postprandial hypotension), and after prolonged bed rest (deconditioning).*
(long term) Bed Rest

• Relative reduction of circulating plasma volume due to a cardiopulmonary re-distribution (increase of pre-load, right atrial distension and natriuretic peptide release)

• Left ventricular remodelling (↓ of ventricular dimension and ↓ of CO)

• Reduction of leg muscle tissues particularly in the elderly
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OH in Parkinson disease

- OH affects about 58% of patients, among them 62% reports symptoms and signs of orthostatic intolerance including orthostatic syncope

- Alterations in cardiac sympathetic innervation (cardiac SPECT with sympathicomimetic amines $^{123}$MIBG and PET scanning with F-dopa)

- Alterations in sympathetic autonomic control to the vessels
EFFECTS of 75° HEAD-UP TILT

- **Controlls**
- **PD (without OH)**
- **PDOH (with OH)**

Source: Barbic et al Hypertension 2007;49:120
Basic cardiovascular autonomic function tests
(usefulness in neurogenic OH)

• Valsalva manoeuvre & deep breathing
• Tilt test
• Ambulatory BP monitoring
Control

Resp 0.1 Hz

AP

RR (sec)

Resp

SA (HR max - min): 26 (v.n.>8)

SA (ratio): 1.44 (v.n.>1.2)
Control

Resp 0.1 Hz

AP

RR (sec)

Resp

AP

RR (sec)

Resp

SA (HR max - min): 0.6 (v.n.>8)

SA (ratio): 1.01 (v.n.>1.2)
Overshoot absence during phase 4

Valsalva ratio
HRmax / HRmin
1.01 (v.n. >1.4)
Pure Autonomic Failure (PAF)
ABPM

Nocturnal dipping

Non-dipping

Reverse dipping
Treatment of syncope: **Orthostatic hypotension**

- **Syncope due to orthostatic hypotension**
  - **Education, life-style measures** (Class I)
  - **Adequate hydration and salt intakes** (Class I)
  - **Stop/reduce vasoactive drugs** (Class IIa)
  - **if symptoms persist**
    - **Counter-pressure manoeuvres** (Class IIa)
    - **Compression garments** (Class IIa)
    - **Head-up tilt sleeping** (Class IIa)
    - **Midodrine** (Class IIa)
    - **Fludrocortisone** (Class IIa)
Non- Pharmacologic Measures

• Eliminate causes of ipovolemia and increase intravascular volume (i.v saline infusion; H₂O and NaCl per os)

• Early mobilisation of patients and FKT, reduce the time of bed rest

• Physical countermaneuvers (leg-crossing, toe-raise, thigh contraction)

• Devices to Decrease Venous Pooling Waist-high compressor stockings (30 to 40 mmHg) or abdominal binders

• Caffeine before eating and reduction of carbohydrate intake (at lunch)

• Water per os bolus treatment (500 ml of H₂O) increase BP of >20 mmHg for about 2 hours (J.Jordan, Circulation 2000; 101: 504-9)
Effects of $H_2O$ intake while supine in neurogenic OH

<table>
<thead>
<tr>
<th></th>
<th>SAP (mmHg)</th>
<th>DAP (mmHg)</th>
<th>HR (b/min)</th>
</tr>
</thead>
</table>

* Micturition

Time (min.)

H$_2O$ (480 ml)
Pharmacologic Measures

- Midodrine (directly-acting α1-agonist) improve orthostatic hypotension and orthostatic intolerance (JAMA 1997;277:1046); 2,5-10 mg 2-4 times /day

- Fludrocortisone (has high Na+ retention activity, expands plasma volume and increases α-adrenoreceptor sensitivity) 0,05-0,3 mg/day.

- Pyridostigmine (cholinesterase inhibitor improve ganglionic transmission). It exerts its action primarily when the patient is standing without worsening supine BP (Lancet Neurol 2008; 7(5):451-458; Arch Neurol 2006;63:513); 30-60mg 3 times/day.

- Droxidopa prodrug converted centrally and peripherally to norepinephrine, recently approved by the FDA 100-600 mg 3 times/day.
Other drugs

Paroxetine (inhibitor of serotonin reuptake) 10-20 mg/day
Reboxetine (inhibitor of norepinephrine reuptake) 2-4 mg/day
Autoimmune Autonomic Ganglionopathy

25-50% of patients with symptoms of primary autonomic failure (as PAF) has circulating antibodies to the ganglionic cholinergic receptors, in these case an autoimmune mechanism is suspected.

Dosage of antibodies to the nicotinic ganglionic cholinergic receptors alfa3 and alfa7 sub-units.

Repetitive sessions of antibodies plasma removal and administration of immunosuppressive drugs produce a significant long term improvement of dysautonomia symptoms including OH and syncope.
Case Report

Long-term cardiovascular autonomic and clinical changes after immunoglobulin G immunoabsorption therapy in autoimmune autonomic ganglionopathy

Franca Barbic\textsuperscript{a,d}, Franca Dipaola\textsuperscript{a,d}, Francesca Andreetta\textsuperscript{b}, Enrico Brunetta\textsuperscript{a,d}, Laura Dalla Vecchia\textsuperscript{c}, Renato Mantegazza\textsuperscript{b}, Raffaello Furlan\textsuperscript{a,d}, and Carlo Antozzi\textsuperscript{b}

Journal of Hypertension 2017, 35:1513–1520