Prevalence of orthostatic hypotension

Abstract Orthostatic hypotension (OH) is defined as a fall in blood pressure of at least 20 mmHg systolic or 10 mmHg diastolic when standing or during head-up tilt testing. The prevalence of OH increases with age, with disorders that affect autonomic nerve transmission, and with increasingly severe orthostatic stress. In normal elderly subjects, the prevalence of OH is reported to be between 5 and 30%. The actual prevalence depends on the conditions during diagnostic testing, such as the frequency of blood pressure recordings, the time of day and the degree of orthostatic stress. Elderly subjects are often taking medications, such as antihypertensives and diuretics that can cause or aggravate OH. Neurological diseases such as diabetic neuropathy, Parkinson’s disease, multiple system atrophy and the autonomic neuropathies further increase the likelihood of OH. The development of OH in normal subjects is associated with an increased mortality rate. OH in diabetes is also associated with a significant increase in mortality rate.

Keywords orthostatic hypotension · aging · neuropathy · mortality · prevalence · autonomic nervous system

Orthostatic hypotension (OH) is a dynamic state and not a disease in itself or necessarily a pathologic entity. Cross-sectional prevalences primarily reflect the influence of age (Fig. 1), but to some degree also reflect the effects of medications, the degree of orthostatic stress, and the presence of abnormalities of the autonomic nervous system. This review considers the prevalence of OH in particular settings (such as long-term care facilities and outpatient clinics), and the prevalence of OH in patients with autonomic disorders associated with OH.

OH in the normal aging population

The cross-sectional prevalence of OH in unselected elders, aged 65 years or older, has been reported to be between 5 and 30% [9, 13, 15, 22, 27]. The difference in these estimates varies due to a number of factors, such as the definition of OH, the segment of the population studied (age range, institutions), the composition of the population (healthy population versus select groups), the influence of medications and the level of orthostatic stress. The prevalence appears to be similar in North America [9], in Japanese in Hawaii [15] and in Finns in Finland [27]. In all of these studies the prevalence of OH increased with age.

Using the current standard of an orthostatic fall in blood pressure by 20 mmHg systolic or 10 mmHg diastolic within 3 min of standing up or during head-up tilt, 5% of the normal healthy population in Rochester, Minnesota has OH [10]. In the a multicenter, observational, longitudinal study by Rutan et al. (1992) in 5,201 men and women aged 65 years...
or older at their initial examination, the prevalence of asymptomatic OH (defined as a minimum fall in systolic BP by 20 mmHg or in diastolic BP by 10 mmHg within 3 min of standing) was 16.2%. When the criteria for defining OH also included those in whom the procedure was aborted due to dizziness upon standing, this prevalence increased to 18.2%. The prevalence of symptomatic OH increased from 14.8% in subjects aged 65–69 years to 26% in subjects 85 years and older, clearly demonstrating the association between OH and aging [22].

**OH and mortality rate**

In a population-based study of 3,522 Japanese Americans in Hawaii aged between 71 and 92 years, Masaki et al. [15] reported that the prevalence of OH was 6.9%, and again that the prevalence increased with age (Fig. 1). They also found that the 4-year age-adjusted mortality rate was higher in those with OH than in those without (56.6 versus 38.6 per 1,000 person-years). With Cox proportional hazards models, after adjusting for other risk factors, OH was a significant independent predictor of 4-year all-cause mortality, with a relative risk of 1.64 (95% CI 1.19 to 2.26). Furthermore, there was a significant linear association between the change in systolic BP fall and 4-year mortality rate ($P < 0.001$), suggesting a dose-response relationship [15].

Rose et al. [21] studied the association between OH and a 13-year mortality among middle-aged black and white men and women from the Atherosclerosis Risk in Communities Study (from the year 1987 to 1989). At baseline, 674 participants (5%) had OH. All-cause mortality was higher among those with (13.7%) than without (4.2%) OH (see Fig. 2). This association was only partly explained by “traditional” risk factors [21].

**OH in defined groups**

Although not true prevalences, the presence of OH in settings such as in nursing homes or outpatient clinics is of interest. If the OH associated with aging is included, the “prevalence” is quite high in subjects older than 70 years of age. Table 1 lists seven prevalences (as percentage of the affected group with OH) in particular settings, taken from studies carried out with similar criteria in subjects who were otherwise generally healthy. These are perhaps the best estimates of the prevalence of OH based on current data. Therefore, a reasonable estimate of prevalence in

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**Fig. 1** The prevalence of OH increases with age. Prevalence rates of orthostatic hypotension (OH) by 5-year age groups (71–74, 75–79, 80–84, and 85+) in the Honolulu Heart Program cohort ($n = 3,522$). Masaki et al. [15]

**Fig. 2** Kaplan–Meier survival curves by OH status. These unadjusted Kaplan–Meier curves for all-cause mortality by OH status show a gradual increase in mortality in those free of OH at baseline, with an overall mortality rate of 12% ($n = 1,478$) over the 13 years follow-up period. For the OH group, by contrast, the slope of the survival curve was considerably steeper, and at the end of the follow-up period, 32% ($n = 217$) of participants had died. Rose et al. [22]
Table 1 Estimated "Prevalence" of OH in certain settings

<table>
<thead>
<tr>
<th>Setting</th>
<th>n</th>
<th>Age (years)</th>
<th>Prevalence (%)</th>
<th>Study Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nursing home</td>
<td>250</td>
<td>61–91</td>
<td>11</td>
<td>Rodstein and Zeman [20]</td>
</tr>
<tr>
<td>Medical outpatient</td>
<td>494</td>
<td>85</td>
<td>24</td>
<td>Caid et al. [8]</td>
</tr>
<tr>
<td>VA Geriatric unit</td>
<td>219</td>
<td>50–99</td>
<td>10.7</td>
<td>Myers et al. [16]</td>
</tr>
<tr>
<td>Medical outpatients</td>
<td>180</td>
<td>65</td>
<td>22</td>
<td>MacErlan and Wilson [12]</td>
</tr>
<tr>
<td>Geriatric unit</td>
<td>273</td>
<td>85</td>
<td>10</td>
<td>Lennox and Williams [8]</td>
</tr>
<tr>
<td>Geriatric unit</td>
<td>247</td>
<td>70</td>
<td>13</td>
<td>Palmer et al. [18]</td>
</tr>
<tr>
<td>Medical outpatient</td>
<td>300</td>
<td>70</td>
<td>6.4</td>
<td>Mader et al. [14]</td>
</tr>
</tbody>
</table>

Data taken from seven studies carried out with similar criteria in elderly subjects who were otherwise generally healthy. From this we can conclude that "prevalence" is between 10 and 30%, *n* mean value, *n*, number of subjects.

ambulant older subjects, diagnosed during testing with simple BP recordings, is between 10 and 30%.

### OH and increasing orthostatic stress

When testing is done repeatedly and under conditions of increased orthostatic stress, the percentage of subjects with OH increases. For instance, Ooi et al. [17] evaluated 991 long stay residents 60 years of age and older who were able to stand and took four sets of supine and standing BP recordings before and after breakfast and before and after lunch. They found that 13.3% of subjects had persistent OH, consistent with the values reported in Table 1. However, they reported that 51.5% of subjects had OH at least once and that OH was most common first thing in the morning [17].

### OH and medications

Another variable that impacts the prevalence of OH in elderly subjects is the effect of medications. In a Veteran Administration study of 342 veterans 75 years or older, 55% (189/342) had OH, of whom 33% and symptoms of orthostatic intolerance, and 52 patients had falls [19]. There was a significant relationship between the presence OH and the number of medications: with no drug 55% had OH; with one drug 58% had OH; with two drugs 60% had OH; with three drugs 65% had OH. The antihypertensives Hydrochlorothiazide (65% OH) and Lisinopril (60% OH), the diuretic Furosemide (56% OH), the antidepressant Trazodone (58% OH), and the alpha-blocker Terazosin (54% OH) had the greatest propensity to cause OH.

### OH and neurological disorders

Neurological disorders that affect the release of noradrenaline can cause OH. The prevalence of OH in autonomic disorders is summarized in Table 2.

### Table 2 Estimated prevalence of OH in different autonomic disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>10–30</td>
<td>Table 1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10%*</td>
<td></td>
</tr>
<tr>
<td>Diabetes-Type 1</td>
<td>8%</td>
<td>Low et al. [10]</td>
</tr>
<tr>
<td>Diabetes-Type 2</td>
<td>4%</td>
<td>Low et al. [10]</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>47%</td>
<td>Allcock et al. [1]</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>45%</td>
<td>Wood et al. [29]</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>59%</td>
<td>Senard et al. [25]</td>
</tr>
<tr>
<td>Other autonomic neuropathies</td>
<td>10–30 per 100,000</td>
<td></td>
</tr>
<tr>
<td>MSA</td>
<td>5–15 per 100,000</td>
<td></td>
</tr>
<tr>
<td>PAF</td>
<td>10–30 per 100,000</td>
<td></td>
</tr>
</tbody>
</table>

*Prevalence for adult combined IDDM and NIDDM for the Rochester Diabetic Cohort for 1997 (P; PJ Dyck)

### Diabetes and OH

In a cohort of adult diabetic patients (insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus) evaluated at the Mayo Clinic (Rochester, Minnesota) from 1987 to 1997, mean age over this decade 60 ± 12 years] 10% had OH. To investigate the association between autonomic function and symptoms of OH a population-based study in 148 diabetic patients (83 with Type 1 diabetes) and 246 healthy controls was conducted. OH symptoms (assessed using the "Autonomic Symptom Profile"—a validated self-reporting instrument), standardized autonomic function tests (cardiovascular, adrenergic, sudomotor function), and a Composite Autonomic Severity Score (CASS, which corrects for the effects of age and gender [11]) were evaluated. A CASS score of 1–3 was used for either sudomotor and cardiovascular functional deficits and 0–4 for adrenergic deficits. Autonomic neuropathy (defined as a CASS score of 1 in at least 2 domains or ≥2 in one domain) was found in 54% of Type 1 diabetes and 73% of Type 2 diabetes. Despite the high prevalence of autonomic dysfunction, OH was found in only 8.4% (Type 1) and 7.4% (Type 2) of diabetic patients.

### Autonomic failure and OH

Allcock et al. [1] estimated the prevalence of OH in Parkinson’s disease in a population of 237,564 in the county of Durham (UK). They identified 270 patients with Parkinson’s disease of whom 104 (38.5%) agreed to participate. They reported that 47% had OH [1], a remarkably high incidence. Other reports in Parkinson’s disease outpatient cohorts have estimated the prevalence of OH to be between 16 and 58% [25, 29]. OH is an integral feature of the autonomic neuropathies, pure autonomic failure (PAF), and multiple
system atrophy (MSA, Shy-Drager syndrome). The prevalence as cases per 100,000 is provided in Table 2.

The causes of OH

The causes of neurogenic OH are shown in Table 3. The diseases with the highest prevalence of neurogenic OH, are MSA, PAF, diabetic autonomic neuropathy, autoimmune autonomic neuropathy and paraneoplastic autonomic neuropathies. In specialist spinal cord injury practices, tetraplegia is a common cause of OH.

In a prospective study of 90 consecutive patients referred with suspected OH, evaluated at the Mayo Autonomic Laboratory, and confirmed to have OH, the diagnoses were:

- PAF: 33%
- MSA: 26%
- Idiopathic (autoimmune autonomic neuropathy): 17%
- Diabetic autonomic neuropathy: 14%
- Miscellaneous: 8%
- Olivo-ponto-cerebellar atrophy: 2%

The cause of OH and prognosis

The prognosis depends on the specific disorder. Patients with classic MSA have a median survival of about 7 years from the time of diagnosis [2]. Wenning et al. [28], however, reported a median survival of 9.5 years, calculated by Kaplan–Meier analysis. Similar results have been reported [23], and the sporadic OPCA variety has been suggested to have a longer survival than the striatonigral variety [23]. The differences in survival time reported most likely relates to the criteria used to define MSA.

The downhill course of patients with MSA is marked by increasing rigidity, urinary incontinence, and inspiratory stridor, which may require tracheotomy. Death in MSA is commonly due to respiratory obstruction or failure after worsening rigidity, akinesia, and bladder disorder. With the appreciation of a spectrum of severities, an attempt has been made to relate the severity and distribution of autonomic and non-autonomic involvement to the outcome. We reviewed the clinical and autonomic features of all patients with extrapyramidal and cerebellar disorders studied in the Mayo Autonomic Reflex Laboratory from 1983 to 1989 [24]. OH, percentage of anhidrosis on thermoregulatory sweat test, quantitative sudomotor axon reflex test, forearm resistance response and heart rate response to deep breathing strongly regressed with severity of clinical involvement. The severity and distribution of autonomic failure at the time of first evaluation was predictive of a greater rate of progression 2 years later. Saito et al. [23] came to the same conclusion. The earlier and more severe the autonomic nervous system involvement (and to a lesser extent the striatonigral system involvement) the poorer the prognosis.

Information on the clinical features, progression and outcome in PAF is somewhat limited. Some patients with PAF have continued relatively symptom free for many years, with standing blood pressures as low as 80 mmHg. The natural history of PAF is that of a slow progression taking place over some 10–15 years [2]. However, we should take into account the difficulty in diagnosing PAF. About 10% patients originally thought to have PAF turn out to have MSA. Moreover, some patients are misdiagnosed as PAF, and later found to have autoimmune autonomic ganglionopathy [6] with ACh acetylcholine receptor antibodies.

The development of OH worsens the prognosis of patients with diabetic neuropathy. Ewing et al. [4] reported a mortality rate of 50% at 2½ years in patients with symptomatic diabetic autonomic neuropathy. However, these patients had long-standing
clinical autonomic neuropathy and died of renal failure. Subsequent studies suggest that autonomic failure worsens prognosis, but less dismally than was originally thought [5]. The clinical and laboratory features of 229 patients with primary systemic amyloidosis seen at the Mayo Clinic reported that median survival from the time of diagnosis for patients with peripheral neuropathy, carpal tunnel syndrome, OH and cardiac failure was 60, 45, 9.5, and 6.5 months, respectively [7].

We have reviewed the Mayo Clinic experience with idiopathic autoimmune autonomic neuropathy. Patients seem to improve substantially over the first year followed by a slower rate of improvement over the subsequent 4 years [26]. Overall, approximately 1 in 3 patients makes a good functional recovery. However, the majority of patients are left with a chronic debilitating illness with significant residual deficits.

For patients with OH associated with aging, the coexistence of OH is associated with a worse prognosis [15].

Concluding thoughts

OH is a dynamic entity, it is frequent, and increases with age. Indeed, it is likely to be present in most of the elderly under circumstances of increased orthostatic stress. Its prevalence is further increased in certain neurologic disorders. The presence of OH worsens prognosis and increases mortality.

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References